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TECHNICAL NOTE

QUANTUM GENETICS AND THE APERIODIC SOLID.

SOME ASPECTS ON THE BIOLOGICAL PROBLEMS OF HEREDITY, MUTATIONS, AGEING, AND TUMORS IN VIEW OF THE QUANTUM THEORY OF THE DNA MOLECULE

by

Per-Olov Löwdin

Quantum Chemistry Group
For Research in Atomic, Molecular and Solid-State Theory
Uppsala University, Uppsala, Sweden

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CONTENTS

ABSTRACT

Recent development in biology has shown that deoxyribonucleic acid (DNA) is the hereditary substance which carries the genetic message in the cell. After a brief historical review of the development, the structure of DNA is discussed in greater detail.

According to Watson-Crick's stereo model, the DNA-molecule is a double helix with the two sugar-phosphate chains held together by a sequence of pairs of nucleotide bases (A, G, T, C) joined by hydrogen bonds. The pairing is specific (A - T, G - C) and, in the cell duplication, each half of the helix is forming its own complement. It is believed that the genetic information is contained in the sequence of base pairs which is preserved through this arrangement. The possible mechanisms for the replication and transcription of the genetic message through DNA-duplication and RNA-formation are discussed. It is further shown that, according to quantum mechanics, there is a finite probability that the normal base pairs A - T and G - C may spontaneously go over into the tautomeric pairs A^* - T^* and G^* - C^* through a "proton exchange" along the hydrogen bonds. Since the tautomeric bases have another pairing pattern (A^* - C, G^* - T, C^* - A, T^* - G), the proton exchange leads inevitably to errors in the genetic base sequence in the next duplication. This mechanism may be responsible for the occurrence of spontaneous mutations, ageing (considered as a loss of useful genetic information through accumulation of errors), and the occurrence of sponteneous cancer when the accumulated errors have passed a critical limit in a certain direction.

1. INTRODUCTION

The cell may be considered as the fundamental biological unit. The cell consists of a nucleus surrounded by cytoplasm, in which further various bodies may occur. The nucleus is responsible for the most important properties of the living cell. The fundamental properties of the nucleus are determined by the chromosomes containing the genes, and these consist essentially of giant organic molecules known as deoxyribonucleic acid (DNA), which are the essential carriers of the genetic information characteristic for the species. Many biological and medical problems are directly related to the properties of these molecules and, since they govern the cell duplication and the protein synthesis, they are of essential importance in the problem of normal growth and ageing as well as in the development of tumors.

After many years of experimental research, the structure of DNA is now well known. According to Wilkins-Watson-Crick's stereo model, DNA consists of a double helix, where the sides or strands are sugar-phosphate chains joined by pairs of nucleotide bases. Each base-pair consists of a purine base and a pyrimidine base held together by two hydrogen bonds. The DNA-problem is greatly simplified by the fact that there are only four nucleotide bases involved: adenine (A), thymine (T), guanine (G), and cytosine (C). The pairing of the bases is further specific in the combinations A-T, G-C, so that each base has a specific complementary base.

It is today believed that the genetic information is contained in the sequence of the nucleotide bases attached to one strand of the DNA-molecule, i.e. in a four-letter message of the form A G T C A T T G C A ... . The other half contains the complementary sequence, i.e. T C A G T A A C G T ... , and the double helix consists of two parts which may be compared with a photographic negative and positive. In the mechanism of cell duplication, the hydrogen bonds in the double helix are released, the two DNA-strands become at least partly free and each one produces by means of enzymes and available material its own complement, so that two complete DNA-molecules with the same base sequence as the original one are produced.

The complementary nature of the DNA-molecule explains the stability of the genetic message and how it is propagated at a cell duplication. It also tells that if there is an error in the base sequence and the

2. HISTORICAL DEVELOPMENT OF THE THEORY OF THE HEREDITARY MECHANISM

The present knowledge of the nature of the genetic information in all living materials is the result of the collaboration of many different sciences, and we will start with a brief review of the historical development.

Cell Theory and Genetics. - Optics and the art of lens grinding should perhaps be considered as the first contributor to the modern development, since it led to the construction of the microscope. By means of such an instrument, the cell was discovered by Robert Hooke in 1665. In the beginning of the 19th century, the technique was developed far enough to permit a study of the details of the cell. The cell nucleus was discovered in 1831 by R. Brown, and the cell division was first described by H. v. Mohl in 1835. The general cell theory for plants was formulated by M. J. Schleiden in 1838, and the theory was extended to all living organisms by T. Schwann in 1839. Since this date, the cell theory has had an enormous impact on the entire biology as being one of the most important generalizations used in describing life processes.

At about the same time as Charles R. Darwin published his "Origin of Species" (1859), the Abbot Gregor Mendel made experiments on the hereditary properties of some varieties of garden pea in his cloister in Brünn. In contrast to Darwin's theory of evolution which arose an enormous interest even far outside biology, Mendel's work [1] published in 1865 remained practically unnoticed until the turn of the century.

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1) G. Mendel, Verhandlungen der Naturforschenden Vereins in Brünn 10 (1 1865).

During the meantime, there had been an important development in the study of the cells. Thanks to refined dyeing processes in microscopic technique, one had been able to investigate the cell nucleus in greater detail and discovered the "chromosomes". The specificity of the chromosomes and their behaviour under ordinary cell division (mitosis) and under reductive division (meiosis) was first described by van Beneden, Rabl, Boveri, and Strasburger in 1883 - 1888.

In 1900 Mendel's work on the law of inheritance was rediscovered independently by H. de Vries, C. Correns, and E. Tschermak [2], and was made the basis for the new science of genetics. A big step forward could then be taken by combining genetics with cytology and, assuming that the chromosomes are the essential carriers of the genetic information, one could derive a picture of the hereditary mechanism in complete agreement with Mendel's laws.

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2) The three papers by de Vries, Correns, and Tschermak appear in the same volume of "Berichte der Deutschen Botanischen Gesellschaft" (1900).

In 1902, de Vries discovered the mutations. Even in the most homogeneous biological population, there are always small continuous variations of random character and, in his theory of evolution, Darwin had assumed that these accidental variations would provide sufficient material for the natural selection to work. It turned out, however, that these small continuous variations are not inherited. Instead de Vries found that, even in carefully pure-bred populations, there may be a few offsprings - say one in ten thousand - showing a small but discontinuous change which is then inherited. These "mutants" provide, of course, a still better material for Darwin's natural selection, but the nature of the mutation itself was very difficult to understand. One of the fundamental problems in genetics was hence to explain both the immense stability of the hereditary substance in the chromosomes over thousands of years as well as the occurrence of the discontinuous changes leading to the mutations.

Quantum Theory of Matter. - At this point, it may be worthwhile to review briefly some developments in modern physics. At the end of the 19th century, the classical physics appeared to be quite successful in all its applications except for a few minor discrepancies, for instance in the theory of "black--body radiation", where it seemed impossible to bring the results obtained for the long-wave length part in agreement with those for the short-wave length part. These difficulties were removed in one stroke by Max Planck in 1900 by the assumption that the energy of an harmonic electric oscillator emitting radiation could only be an integer multiple of the "energy quantum" $E = h\nu$, where ν is the frequency of the oscillator and h is the so-called

Planck's constant or quantum of action: $h = 6.625 \times 10^{-27}$ ergsec. Hardly could Planck anticipate that this "quantum hypothesis" would soon change the fundaments of the entire physics and a large part of chemistry. In 1905 Einstein applied the new hypothesis to the electromagnetic waves and, by assuming that the radiation occurs quantized in the form of "wave packets", he could successfully explain the photoelectric effect.

By applying the quantum postulate to Rutherford's atom model, Niels Bohr derived in 1913 his famous theory for the hydrogen atom consisting of an electron circling around a proton. Later the orbits were extended to be ellipses characterized by three quantum numbers (n, ℓ , m). Bohr assumed further that the atom could exist only in certain "stationary states", and that the transitions between these states occurred as discontinuous "quantum jumps" connected with radiation. At this time, no one anticipated any connection between quantum theory and the basic laws of genetics, particularly since the physicists were fully busy extending the new approach to the many-electron atoms.

The Bohr-Rutherford atom model has been compared with a solar system in miniature, where the electrons move in elliptical orbits around a positively charged atomic nucleus of extremely small dimensions. The number of positive fundamental charges in the atomic nucleus is called the atomic number Z and equals the number of electrons in the neutral atom; it can be experimentally measured by means of Moseley's law for the K-line in the X-ray spectra of the atoms (1913).

The rare gases He, Ne, A, Kr, Xe, Rn, ... are elements with the atomic numbers Z = 2, 10, 18, 36, 54, 86, ... , respectively, and, since all these elements are chemically inactive, one can assume that the corresponding electron configurations are particularly stable; they are characterized as "rare gas shells". In 1916, Lewis pointed out that the electrons in an atom are conveniently divided into two groups: the rare gas shell and the valence electrons, of which only the latter are chemically active. By considering the valence electrons in a molecule, Lewis could also show that each covalent chemical bond is associated with an electron pair shared between the two atoms involved. However, any deeper explanation of the stability of such a bond was still lacking and would come only through the further development of quantum theory.

In 1924, Louis de Broglie reversed Einstein's wave-corpuscle parallelism of 1905 by assuming that each fundamental particle (electron,

proton, etc.) is associated with a wave packet and, in this way, he could give a deeper explanation of Bohr's model for the hydrogen atom. However, the full content of the new approach was first realized by Erwin Schrödinger in 1925 who postulated the existence of a certain wave equation for the fundamental particles involved; with this work physics took the step over to wave mechanics or modern quantum theory. It is remarkable that the new theory was at the same time developed independently by two other authors: by Heisenberg in terms of matrices, and by Dirac in terms of q-numbers.

Schrödinger could show that the existence of the stationary states of atoms and molecules was an immediate consequence of the theory, and that these states actually corresponded to the discrete "wave patterns" which were possible with respect to the physical boundary conditions involved. Again the transitions between the states corresponded to discontinuous "quantum jumps" associated with a change in the total energy.

Another important consequence of the new theory was found by Heisenberg in 1927: it turned out that all electrons are in principle identical and indistinguishable, and that this fact leads to a new symmetry law and the so-called exchange phenomenon. By applying the new approach to the electron pair in the covalent bond of the hydrogen molecule, Heitler and London (1927) could show that the energy of this bond is actually stabilized by the identity principle, and that the nature of Lewis' covalent bond hence depends essentially on a typical quantum-mechanical phenomenon, namely the exchange of electrons. This work opened the new field of "quantum chemistry". According to modern quantum theory, it should thus be possible to calculate the stationary states of a given molecule: the ground state, the various isomeric states, and all the excited states. The modern development has shown that the calculations involved may be of an immense order of magnitude, but the important thing is here the fundamental laws and principles.

Mutations as Quantum Jumps. - In the 1930's, Delbrück pointed out the close analogy between the fundamental laws of genetics and of quantum theory: the immense stability of the hereditary substance in the chromosomes over thousand years may indicate that it may be nothing but an immense molecule in a stationary state, and the mutations would then correspond to "quantum jumps" to isomeric forms.

Quantum-mechanical considerations of the type common in reaction kinetics imply that the probability for a quantum jump is roughly propor-

tional to the quantity $\exp(-\Delta E/kT)$, where ΔE is the activation energy from the state under consideration up to the energy threshold leading over to the other state, and kT is the average heat energy. Experimental data for mutations have shown at least a rough agreement with such a type of law, but we will return to this question later.

The Delbrück-model has been discussed in greater detail by Schrödinger in his Dublin lectures (1943) and in his little book "What is Life?" [3], and he points out that the gene in the chromosome fiber may suitably be called an aperiodic crystal. He emphasizes that physicists

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3) E. Schrödinger, "What is Life? The Physical Aspects of the Living Cell" (Cambridge University Press, 1945).

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usually deal with periodic crystals and that, even if solid-state physics experimentally and theoretically is a highly complex and fascinating field where many important results have been achieved, the periodic structure is certainly plain and dull in comparison to an aperiodic crystal. "The difference in structure is of the same kind as that between an ordinary wallpaper in which the same pattern is repeated again and again in regular periodicity and a masterpiece of embroidery, say a Raphael tapestry, which shows no dull repetition, but an elaborate, coherent, meaningful design traced by the great master". For a study of the aperiodic crystal which is the material carrier of life, Schrödinger points to organic chemistry. Let us hence see what has happened on the chemical side.

Chemistry of the Nucleic Acids. - In the beginning of the 19th century there had been a gap between organic chemistry and inorganic chemistry which was bridged by Wöhler's famous synthesis of urea in 1828 showing that "vital forces" from living cells were not absolutely necessary in producing organic compounds. At the same time as the cytologists started discovering the inner details of the cell, it became clear that the laws of ordinary chemistry were valid also within living matter.

The substances in the cytoplasm and in the cell nucleus were analyzed by the chemists and, in the latter, F. Miescher discovered in 1868 certain compounds which are now called "nucleic acids". Our knowledge of these compounds has been further enriched through the work by Hammarsten, Caspersson, and many others, and for a survey we would like to refer to

the comprehensive book by Davidson [4].

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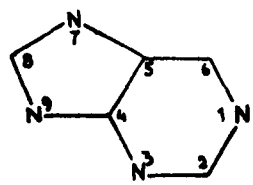
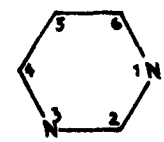
4) J.N. Davidson, "The Biochemistry of the Nucleic Acids" (Methuen and Co., 4th edition, London 1960).

Through later research it has become clear that the nucleic acids are not confined to the cell nucleus but may be found also in the cytoplasm. Today, one distinguishes between two types of nucleic acids: deoxyribonucleic acids (DNA) and ribonucleic acids (RNA). The main constituents of these compounds are aromatic nitrogen bases, pentose sugars, and phosphate groups. The nitrogen bases are of either purine or pyrimidine type:



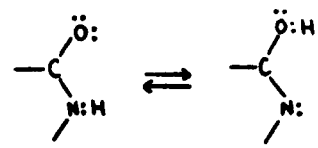
Purine



Pyrimidine

In the figures, we have also indicated the conventional numbering system of the ring atoms involved. In DNA, there are four main bases: adenine (A) and guanine (G) of purine type, and thymine (T) and cytosine (C) of pyrimidine type. RNA contains the same bases, but thymine is here replaced by uracil (U). There are also some small biological variations, and the detailed chemical structure of all the common bases is given in Fig. 1.

It should be observed that all the bases have the simple form of isomerism called "tautomerism" and which may be characterized by moving a proton from one electron pair to another. There are two main types, the keto-enol tautomerism:

keto-form  enol-form

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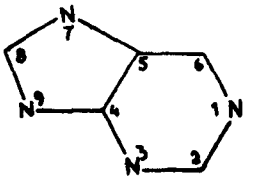
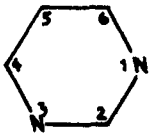


Purine



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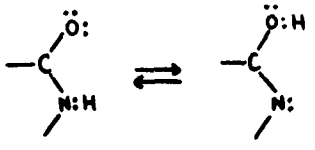
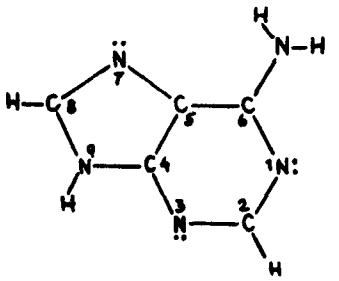
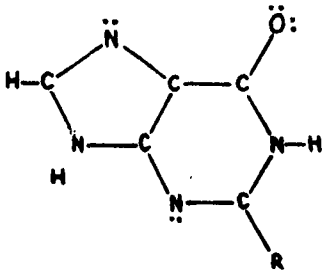
keto-form  enol-form

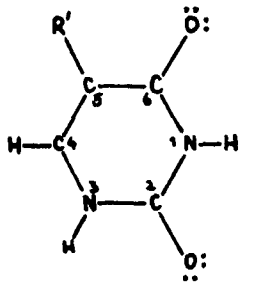


Adenine (A)



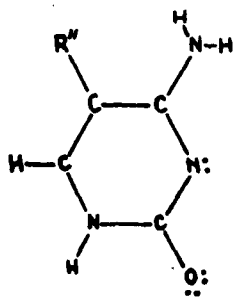
Guanine bases:

R { - NH_2 Guanine (G)
R { - H Hypoxanthine



Thymine bases:

R' { - CH_3 Thymine (T)
R' { - H Uracil (U)
R' { - Br Bromuracil (baseanalog)

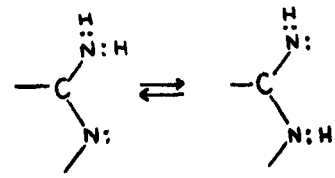


Cytosine bases:

R'' { - H Cytosine (C)
R'' { - CH_3 Methylcytosine
R'' { - Br Bromcytosine (baseanalog)

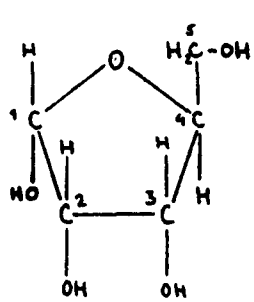
Figure 1. Chemical structure of the common bases and some of the baseanalogs; in addition to the σ-skeleton indicated by the figure, there is also a π-electron cloud corresponding to the conventional double bonds. The double dots : indicate electron lone pairs which attract protons and will participate in hydrogen bonding.

and the amino-imine tautomerism:

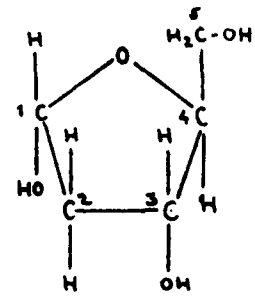
amino-form  imine-form

In Fig. 1, the keto- and amino forms have been considered as standard.

It was rather early found [4] that the pentose sugar groups occurring in the nucleic acids were riboses of the following type:



ribose (RNA)



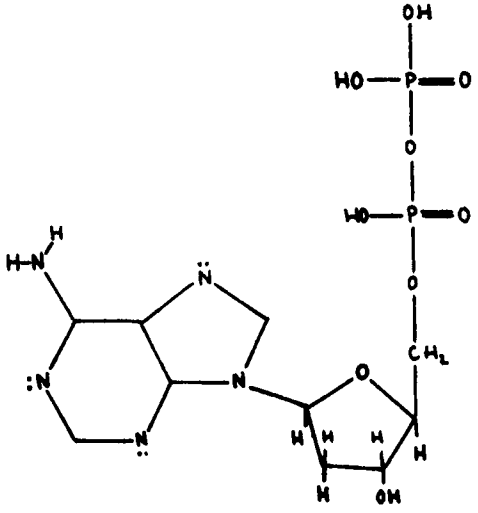
2-deoxyribose (DNA)

In the deoxyribose, the oxygen attached to the 2-position in ribose has been removed.

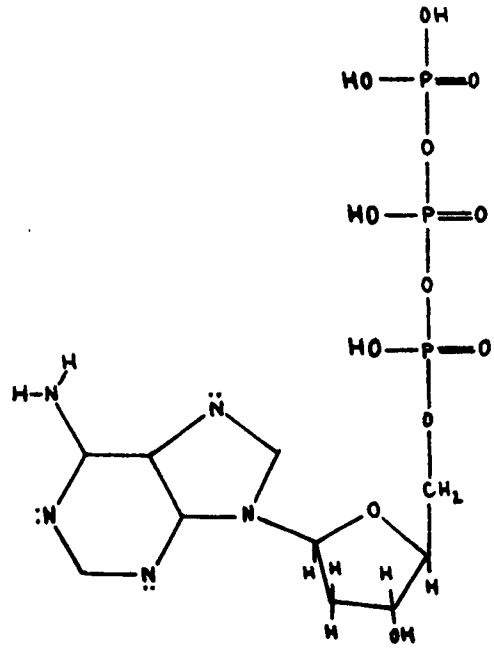
A nitrogen base may be condensed with a ribose or deoxyribose to form a nucleoside, and one distinguishes between ribonucleosides and deoxyribonucleosides. Adenosine, guanosine, cytosine, and uridine are the ribonucleosides formed from adenine, guanine, cytidine, and uracil, respectively, whereas thymidine is conventionally the deoxyribonucleoside formed from thymine. Experimental evidence has shown that, in the purine nucleosides, the sugar group is attached in the N_9-position, whereas, in the pyrimidine nucleosides, the sugar is attached in the N_3-position. In both cases only the β-configuration occurs in nature [4].

The phosphoric esters of the nucleosides are called nucleotides, and one distinguishes between ribonucleotides and deoxyribonucleotides. One has

introduced the symbols MP, DP, and TP for the mono-, di-, and tri--phosphates, respectively, so that ATP means adenosinetriphosphate. It should be observed, however, that the symbols are not unique, and that it is necessary to indicate the positions (2', 3', and 5' in the ribonucleosides, for instance) where the phosphate groups are attached. A symbol without position indication is conventionally assumed to mean a compound with the phosphate group (or groups) attached to the 5' position. For example:



ADP

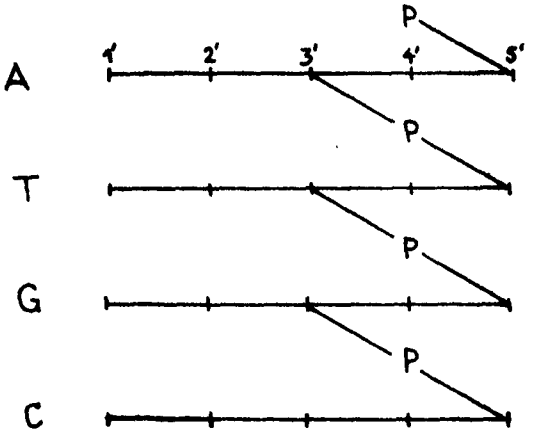


ATP

The adenosinetriphosphate (ATP) is famous in biochemistry as the main source of energy easily available in the cell; under release of energy the molecule is transformed into ADP and a phosphate group. It should finally be observed that a "d" in front of a molecular symbol indicates that one deals with a deoxyribonucleotide, as for instance dAMP, dGMP, ... etc.

Experimental research has revealed [4] that the nucleic acids are polynucleotides formed from the monophosphates AMP, GMP, CMP, TMP,

etc., obtained by linking the phosphate group of one nucleotide to the OH--group of the sugar ring in the next nucleotide, hence leading to a chain structure. The chemical structure of the main mononucleotides are given in Fig. 2, and the chain structure is indicated in Fig. 3. As short-hand for such a compound, one has used the notation:



where each horizontal line indicates a specific nucleoside (with the positions 1', 2', 3', 4', and 5' in the pentose chain) and P the phosphate link between the successive nucleosides; the bases involved are indicated by the letters to the left. Until the end of the 1940's, one used to believe that the nucleic acids contained equimolecular amounts of all of the four main bases and hence showed a tetranucleotide structure of a high degree of periodicity. This hypothesis is now completely abandoned after a most remarkable development in the field of genetics.

DNA as Carrier of Genetic Information. - One of the most interesting discoveries within the field of immunology was the transformation principle found by Griffith in 1928 in his work concerning the properties of pneumococci. He could show that non-virulent living pneumococci could obtain virulent properties by adding extract from the dead cells of virulent species, which indicated that the transformation was achieved by some chemical compound or compounds characteristic for the virulent type. After many years of research, Avery [5] could in 1944 show conclusively that the compound in-

5) O.T. Avery, C.M. MacLeod, and M. McCarty, J. Exp. Med. 79, 137 (1944).

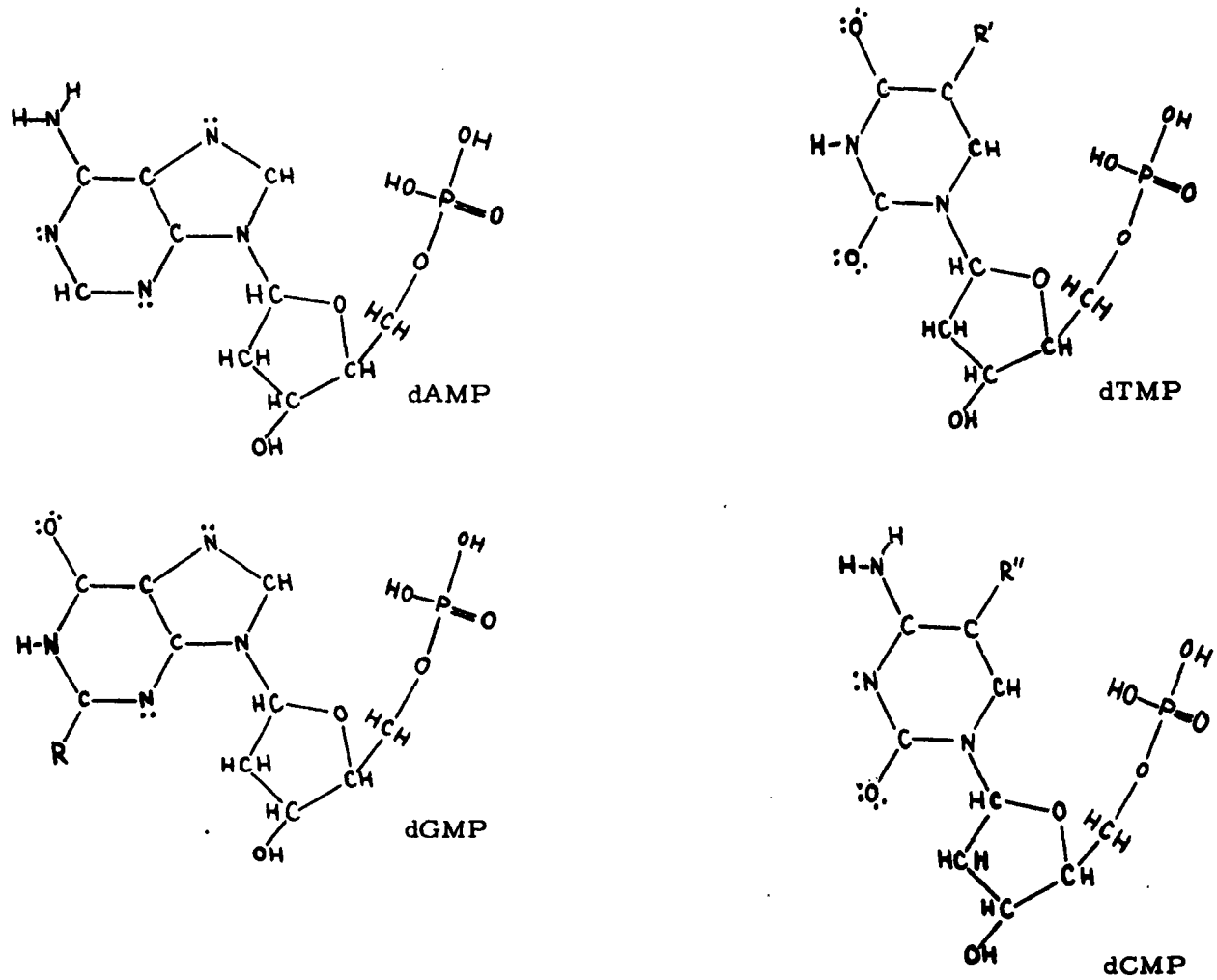


Figure 2. The nucleotides which are the building stones of DNA; the explanation of the radicals R, R', and R" is given in Fig. 1. Note that all the sugar-links are of β-type.

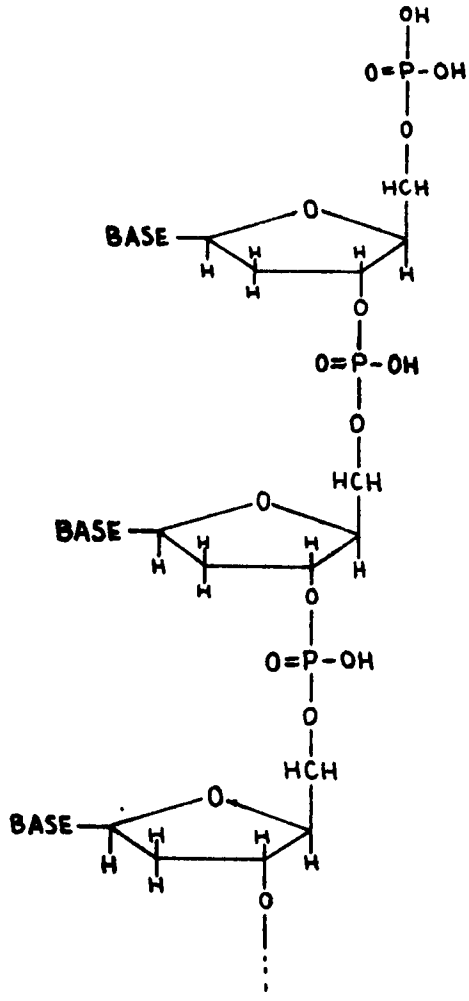


Figure 3. Chain structure of a poly-deoxyribonucleotide. The phosphate-linkage goes between the 5' position in one sugar to the 3' position in the next sugar.

volved in the transformation was DNA. He could also show that transformations may quite generally be induced in a culture of organisms by adding DNA extracted from a mutant, and that DNA hence seems to be the essential carrier of the genetic information. This result seemed like a shock to most scientists involved, since one could hardly believe that a strictly periodic tetranucleotide structure could carry any information of the type required.

The solution of this mystery came in 1950 through the work by Chargaff [6] and his collaborators who studied the molar proportions of the

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6) E. Chargaff, F. Magasanik, E. Vischer, C. Green, R. Doniger, and D. Elson, J. Biol. Chem. 186, 51 (1950); E. Chargaff, Experientia 6, 201 (1950); see also E. Chargaff, "The Nucleic Acids", Vol. I, 307 (Edited by E. Chargaff and J.N. Davidson, Academic Press, New York 1955).

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nucleotide bases in DNA and RNA by means of paper chromatography and could show that the tetranucleotide-hypothesis was completely false. Instead they found that, in DNA, the two bases adenine and thymine occur with the same molar content and that the same is true for the two bases cytosine and guanine, so that

$$\frac{A}{T} = \frac{C}{G} = 1. \qquad (1)$$

On the other hand, the ratio of adenine to guanine varies greatly in DNA from different sources. For RNA, they found the somewhat looser rule that the molar content of adenine and cytosine together equals the molar content of guanine and uracil, so that

$$A + C = G + U. \qquad (2)$$

Through this work, it became clear that the DNA-molecule may have the character of the "aperiodic solid" discussed by Schrödinger [3] in 1943, and that the genetic message may be contained in the four-letter code-script involving the four bases A, T, G, and C along a polynucleotide chain. The result agrees very well with Schrödinger's idea that the genetic code

should consist of a well-ordered association of atoms having the stability of a molecular arrangement and with his statement: "Indeed, the number of atoms in such a structure need not be very large to produce an almost unlimited number of possible arrangements."

3. STEREOSTRUCTURE OF DNA AND THE CONNECTION WITH ITS BIOLOGICAL FUNCTIONING

The Wilkins-Watson-Crick Model of DNA. - The stereostructure of the nucleic acids had for a long time been an important problem, and its study was further intensified after the discovery that the DNA-molecule was the carrier of the genetic information in the cell. The rough structure of the poly--nucleotide chain had been revealed by purely chemical means, see Fig. 3, and refined physical-chemical methods had shown that the molecule was about 20 Å thick and many thousands of ångströms in length and hence had a remarkable fiber structure.

The details of the atomic structure could now be investigated by means of X-ray analysis. This technique originally developed for crystals by von Laue and the Braggs had been used successfully by Pauling [7] and his collaborators in 1951 to study the proteins and had led to the discovery of the helical structures and the importance of the hydrogen bonding. By means of X-ray analysis of the polynucleotides, Furberg [8] had determined

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7) L. Pauling, R.B. Corey, and H.R. Branson, Proc. Nat. Acad. Sci. U.S. 37, 205 (1951); L. Pauling and R.B. Corey, ibid. 37, 251 (1951).

8) S. Furberg, Acta Cryst. 3, 525 (1950); Acta Chem. Scand. 6, 634 (1952).

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the dimensions of the sugar-phosphate backbone and the bases, and he suggested that the structure would be a single helix with a radius of approximately 10 Å. Further X-ray data for DNA were obtained by Wilkins [9] and

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9) M.H.F. Wilkins, A.R. Stokes, and H.R. Wilson, Nature 171, 738 (1953).

his collaborators and, on the basis of these results, two groups independently suggested that DNA would be a double helix having the sugar-phosphate chain in the outside of the helix, namely: Wilkins [10] et.al. and Watson-Crick [11]. The latter made also a careful study of the hydrogen bonding in the structure and its biological implications which has been of fundamental importance for the entire development in this field during the last decade.

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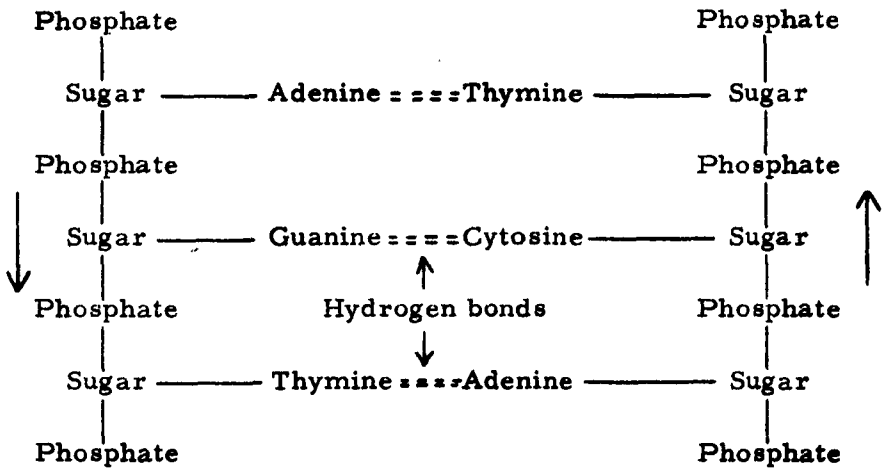
10) M.H.F. Wilkins, W.E. Seeds, A.R. Stokes, and H.R. Wilson, Nature 172, 759 (1953). See also M.H.F. Wilkins, "Biological Structure and Function", Proc. Int. Symp. Stockholm 1960, p. 13 (Academic Press, New York 1961).

11) J.D.H. Watson and F.H.C. Crick, Nature 171, 737, 964 (1953); F.H.C. Crick and J.D. Watson, Proc. Roy. Soc. London A223, 80 (1954).

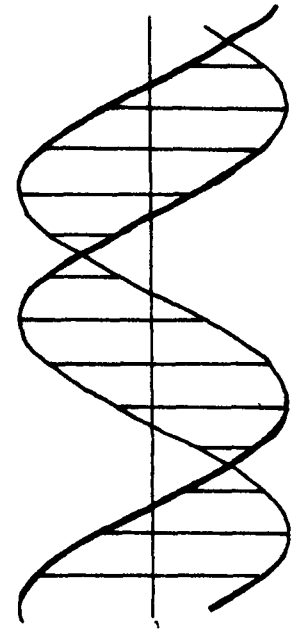
According to this stereo-model, the DNA-molecule consists of a double helix formed by two sugar-phosphate chains of the classical type (see Fig. 3) held together by a sequence of base pairs joined by (at least) two hydrogen bonds; see Fig. 4. Each base pair is approximately a planar conjugated system perpendicular to the long axis of the helix, and it consists of a purine base and a pyrimidine base attached to the sugar groups in the conventional way. The bases are assumed to exist in their keto- and amino--forms, respectively, and the hydrogen bonding is then unique so that adenine is always attached to thymine (A-T) and cytosine to guanine (C-G) in complete agreement with Chargaff's experimental result (1); see Fig. 5.

The double helix has a diameter of approximately 20 Å; each helix makes a full turn after an axis translation of 34 Å containing 10 base pairs, and there is hence a translation of 3.4 Å per base pair and a roation of 36°. Since the sugar linkage is solely of the β-type, both helices are necessarily right-handed and the sugar-phosphate chains run in opposite directions.

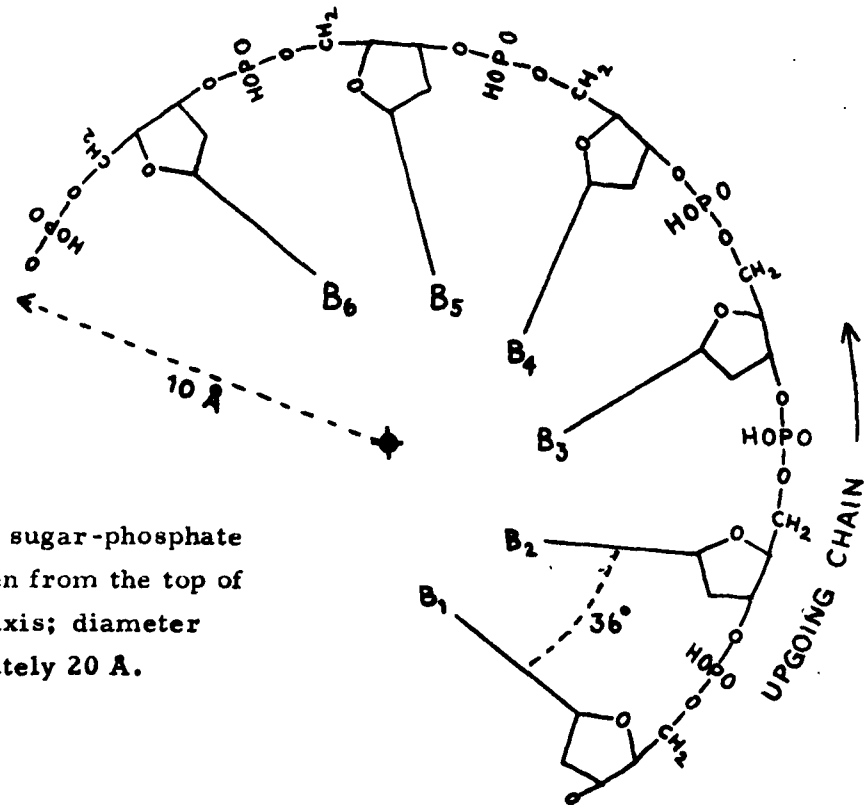
Complementarity and DNA-duplication. - The Watson-Crick model implies that each base B has its specific complementary base B' and, if one strand has the base sequence $B_1\ B_2\ B_3\ B_4 \ldots$, the other strand has the complementary sequence $B_1'\ B_2'\ B_3'\ B_4' \ldots$. It should be observed that the



Linear representation of the DNA-molecule

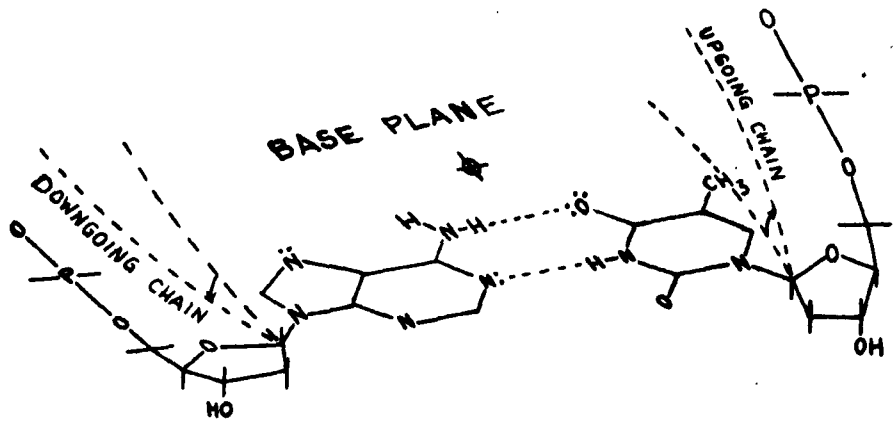


Double helix of DNA

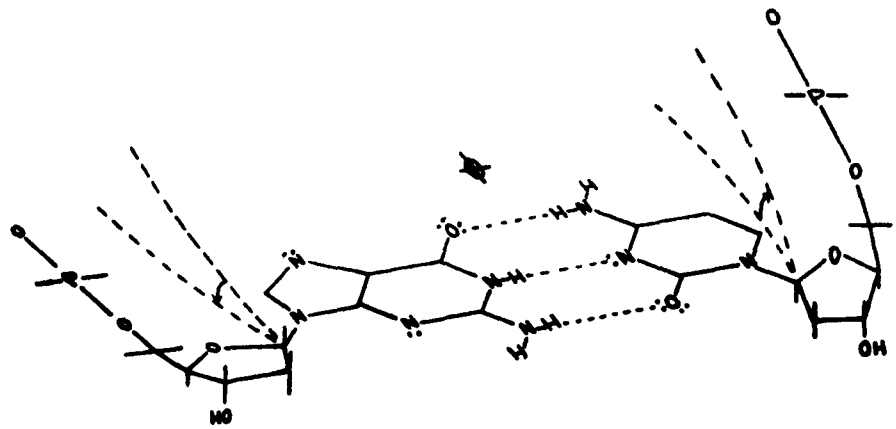


One of the sugar-phosphate chains seen from the top of the helix axis; diameter approximately 20 Å.

Figure 4. Schematic structure of DNA.



A - T base pair



G - C base pair

Figure 5. The normal base pairs occurring in DNA.

complementarity concept depends not only on the hydrogen bonding but also on steric factors: a short pyrimidine base can join only a long purine base, and vice versa, to fit the dimensions of the double helix.

The genetic message in DNA is contained in each one of the two strands in complementary form. Before the cell division, the DNA-molecules should in some way be duplicated and, according to Watson-Crick, the double helix starts unwinding at the same time as each strand starts building its own complement giving rise to two identical DNA-molecules containing the original genetic information, see Fig. 6. The basic principle is exceedingly simple, but the actual mechanism involved may be complicated; this problem will be further discussed in Sec. 6.

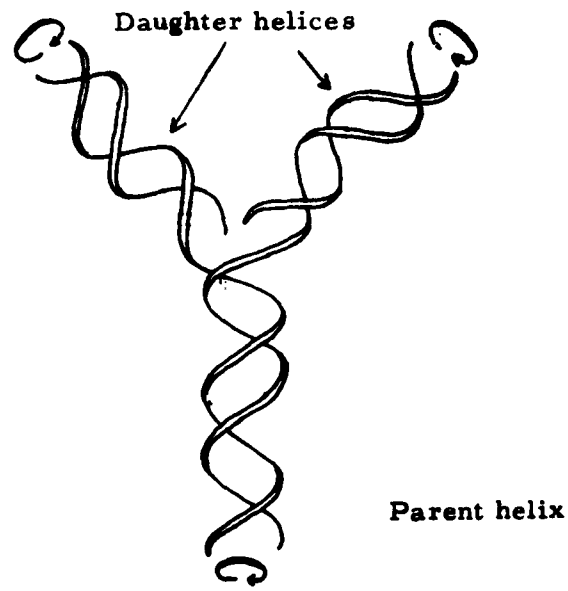
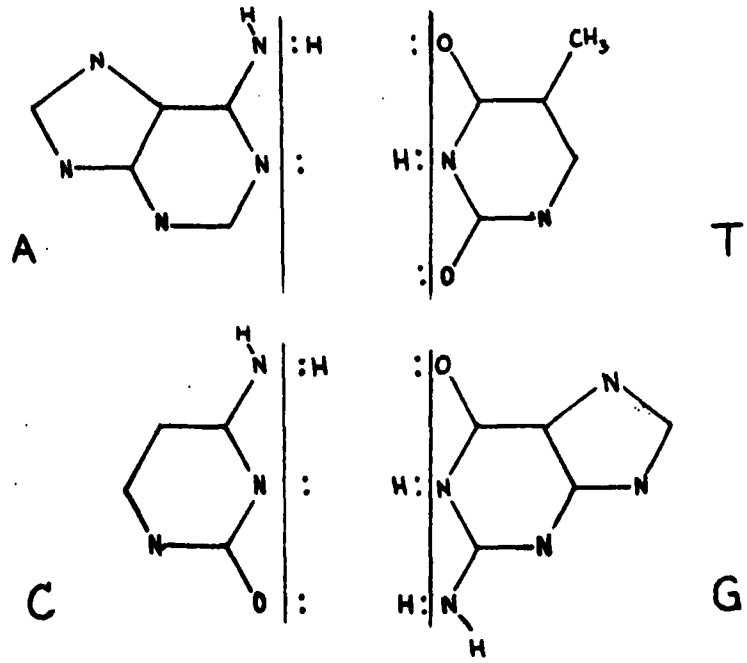


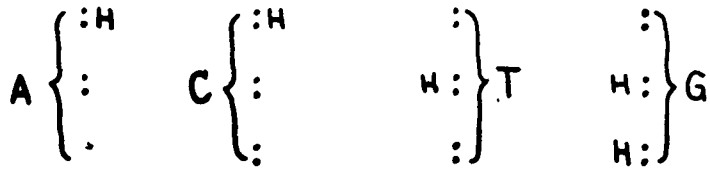
Figure 6. Replication of DNA according to Watson and Crick; winding mechanism after M. Delbrück and G. S. Stent.

Complementarity, Tautomerism, and Mutations. - It is clear that, according to Watson-Crick's model, the complementarity property of the bases is essential for both the stability of the genetic code and for the duplication mechanism.

In order to study the concept of complementarity in greater detail, it is worthwhile to consider the parts of the bases which take part in the formation of the hydrogen bonds; see also Fig. 5:



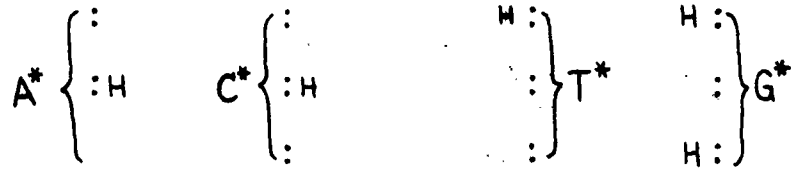
Writing the bases in this particular way, we can introduce the following short-hand for the "proton-electronpair" code:



The bases A and C have equivalent codes (with respect to the upper two positions) and the same is true for T and G. In these figures, we have emphasized the electron lone pairs : and the protons H, and we note that a hydrogen bond is essentially a proton shared between two electron lone

pairs associated with different atoms.

In addition to the normal forms, we will now also consider the previously mentioned tautomeric forms obtained by moving a proton from the upper lone pair to the middle one, or vice versa. Denoting the imine forms of A and C by A^* and C^*, respectively, and the enol forms of T and G by T^* and G^*, respectively, we obtain the following "proton-electronpair" codes:



From a study of the hydrogen bonds, it is now clear that A^* will no longer combine with T but with C, etc., so that one obtains the combinations

$$A^* - C, \quad A - C^*, \quad G^* - T, \quad G - T^*.$$

This means that the complementarity between the bases is completely changed, and the movement of a single proton within a base will in this way influence the genetic message and introduce an error at the first cell duplication, according to the following scheme:

original sequence:	AGTCATTGCA
tautomeric change:	$AGT^*CATTGCA$
complementary sequence:	TCGGTAACGT
new sequence:	AGCCATTGCA

The general diagram below gives a comparison between the normal and the tautomeric replication of the single bases with the complementary base in the middle:

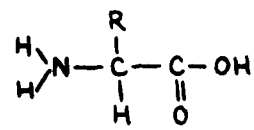
Normal	Tautomeric
A - T - A	A^* - C - G
T - A - T	T^* - G - C
G - C - G	G^* - T - A
C - G - C	C^* - A - T

The genetic error undergoes "biological amplification" by the factors 2, 4, 8, 16, ... and may hence soon become recognizable.

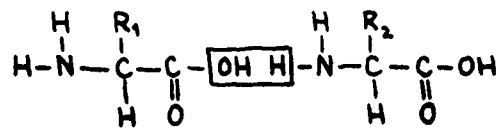
Watson and Crick [11] have suggested such a mechanism to explain the mutations: "Spontaneous mutations may be due to a base occassionally occurring in one of its less likely tautomeric forms". We note that this is in complete accordance with the general idea expressed by Delbrück and discussed by Schrödinger [3]. The "quantum jumps" corresponding to the mutations would then be associated with proton transfer within the DNA--molecule, and the quantum-mechanical mechanism involved in such a process will be discussed in Section 5.

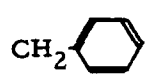
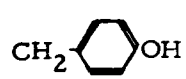
Structure of the Proteins. - The problem is now how the genetic information contained in the DNA-molecule determines the biological properties of the species and individual under consideration. Each species is characterized by its proteins, and of particular importance are the enzymes which catalyze the entire metabolism. The proteins are essentially linear structures built up from 20 amino acids, and the biochemical properties are determined by the sequence of the amino acids. This sequence must, of course, ultimately be determined by the base sequence in DNA, and the question of the connection between these two linear arrangements gives rise to the coding problem.

Let us start with a brief review of the chemical background. An amino acid is characterized by the structure:



where R indicates one of the possible "residues". The 20 residues occurring in nature are listed in Fig. 7. Two amino acids may be joined by the peptide--bond suggested independently in 1902 by Fischer and Hofmeister:



	R	
Glycine	- H	Gly
Alanine	- CH_3	Ala
Valine	- $CH(CH_3)_2$	Val
Leucine	- $CH_2CH(CH_3)_2$	Leu
Isoleucine	- $CH(CH_3)CH_2CH_3$	Ileu
Serine	- CH_2OH	Ser
Threonine	- $CHOH-CH_3$	Thr
Cysteine	- CH_2SH	CySH
Methionine	- $CH_2CH_2SCH_3$	Met
Glutamic acid	- CH_2CH_2COOH	Glu
Aspartic acid	- CH_2COOH	Asp
Lysine	- $(CH_2)_3CH_2NH_2$	Lys
Arginine	- $(CH_2)_3-NH-C(NH_2)=NH$	Arg
Phenylalanine	- CH_2 	Phe
Tyrosine	- CH_2 	Tyr

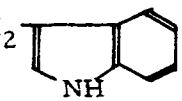
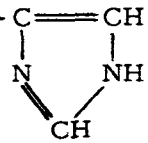
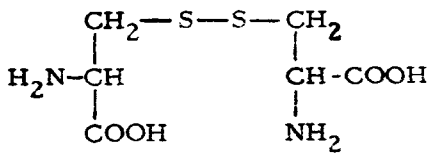
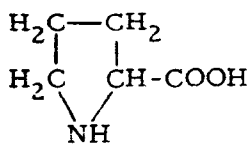
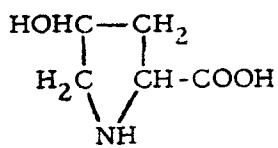
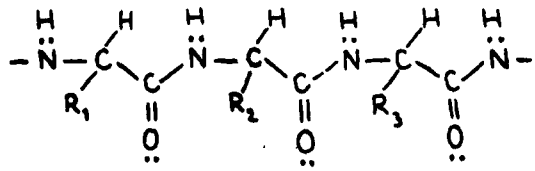
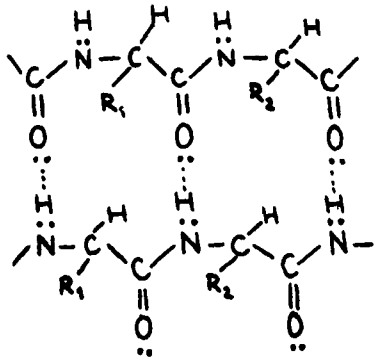
Tryptophan	- CH_2 	Try
Histidine	- $CH_2-C=CH$ 	His
Cystine	$CH_2-S-S-CH_2$ 	CyS-SCy
Proline		Pro
Hydroxyproline		Hypro

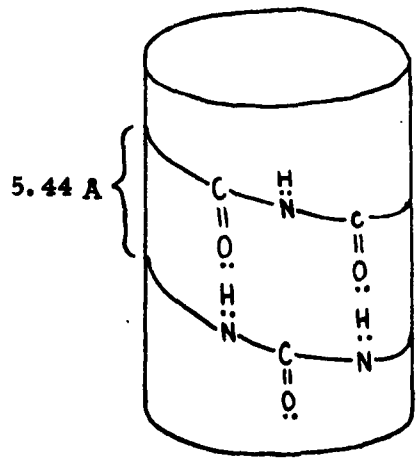
Figure 7. The 20 amino acid residues found in proteins. (The abbreviations are those recommended in the Journal of Biological Chemistry).

and a "polypeptide" has the structure:



A great deal of research in biochemistry has revealed that the proteins are essentially giant polypeptides and, by ingenious methods, one has determined the sequence of the residues R_1, R_2, R_3, ... in some of the most important enzymes. The X-ray analysis by Pauling [7] et.al. has shown that some of the proteins, like α-keratin, have helical structure and are further stabilized by hydrogen bonds between neighbouring chains:





α-helix

All these helices seem to be left-handed in absolute sense, and the residues are pointing out from the cylinder. Other proteins, like myoglobin, have a much more complicated stereostructure [12].

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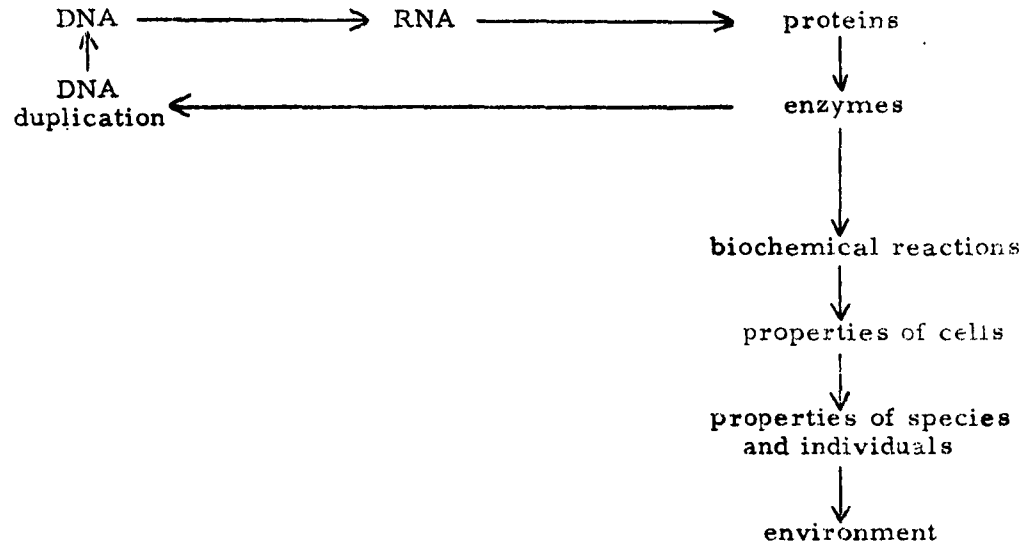
12) See e.g. F.H.C. Crick and J.C. Kendrew, Adv. Protein Chem. 12, 133 (1957); J.C. Kendrew, Revs. Modern Phys. 31, 94 (1959). For a general survey, see P. Berg, Ann. Rev. Biochem., p. 293 (1961).

Role of DNA and RNA in Protein Synthesis. - Let us now return to the coding problem. Through the work by Casperson [13] and others, it had become clear that cells engaged in protein synthesis had a large content of RNA also in the cytoplasm. It is now clear that RNA serves as an intermediate between DNA and the proteins, so that DNA regulates RNA which in turn controls the protein synthesis. Since even the enzymes which catalyze the DNA-duplication are produced in this way, one obtains the following diagram:



which may be characterized as the "growth cycle". Actually, there is a "feed-back" mechanism at several of the other links in the diagram.

Studies of the cytoplasm have revealed that the protein synthesis takes place in small bodies called ribosomes, and that it is regulated by RNA. However, it has turned out that RNA is not a single type of molecule but a complex of molecules with various biochemical functionings [14]. The actual

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13) T. Caspersson, Naturwiss. 29, 33 (1942); "Cell Growth and Cell Function" (Norton and Co., New York 1950); J. Brachet, "Chemical Embryology" (Interscience, New York 1950).

14) See e.g. F.H.C. Crick, Symp. Soc. Exptl. Biol. 12, 138 (1958); M.B. Hoagland, Structure and Function of Genetic Elements, Brookhaven Symp. Biol. No. 12, 40 (1959); J. Brachet, Nature 186, 194 (1960).

genetic information seems to be contained in an enermously long, linear, single-stranded molecule called messenger-RNA which has originally in some way picked up the information at the DNA in the cell nucleus. The dimensions are such that the ribosome is a comparatively small particle in the form of a "ball" or ring gliding along the giant RNA-chain.

For the linear arrangement of the amino acids in the protein, Crick and Hoagland [14] have introduced the so-called adapter hypothesis according to which the amino acids are picked up by small pieces of RNA-molecules called "soluble RNA" or sRNA. "The position of a particular amino acid is then determined not by the amino acid itself but by the hydrogen bonding between the messenger-RNA template and a complementary nucleotide sequence in the sRNA carrying the amino acid". Experimental evidence seems to verify this idea and the role of both messenger-RNA [15] and sRNA [16].

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15) H. Fraenkel-Conrat, A. Tsugita, M. Nirenberg, and J.H. Matthaei, Proc. Nat. Acad. Sci. U.S. 48, 846 (1962).

16) F. Chapeville, F. Lippman, G. v. Ehrenstein, B. Weisblum, W.J. Ray Jr., and S. Benzer, Proc. Nat. Acad. Sci. U.S. 48, 1086 (1962).

Coding Problem. - The problem how the four-letter message in the base-sequence B_1, B_2, B_3, ... in DNA is transferred to the twenty-letter message R_1, R_2, R_3, ... in the proteins is one of the key problems in protein synthesis. Here we will leave the biochemical aspects somewhat aside and instead consider the mathematical problems connected with the transfer of a certain amount of information. It is clear that, since $4 < 20$, a single letter in the base sequence cannot determine a letter in the peptide sequences and, since $4^2 < 20$, the same is true also for pairs of letters. It seems hence necessary that the base sequence in some way is "read" in at least triples of letters but, since $4^3 = 64$, one has then to deal with a code which is either degenerate, partly sense-less, or both.

The coding problem was formulated by Dounce [17], but the first

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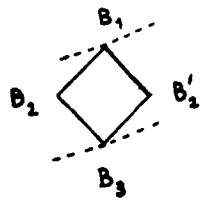
17) A.L. Dounce, Enzymologia 15, 251 (1952).

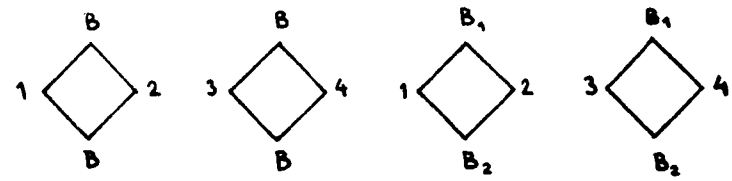
real attempt to solve it was made by Gamow [18]. He had observed that, in the double helix of DNA, there were "holes" in the shallow groove

18) G. Gamow, Nature 173, 318 (1954); Kongl. Danske Vid. Sellsk. Biol. Medd. 22, 3 (1954).

with about the same interspacing as the amino acids in the proteins. Each "hole" was surrounded by 4 base pairs but, since the middle pair consisted of complementary bases, there were actually only three bases involved. The code was hence a "triple code" and, by assuming that it would further be symmetric with respect to the reading direction so that $B_1B_2B_3$ would be equivalent to $B_3B_2B_1$, Gamow could show that it led to 20 independent combinations. These are indicated in the following figure, where, for simplicity, we have denoted the bases by the numbers 1, 2, 3, 4 and assumed that 1-2 and 3-4 are complementary pairs:



Gamow "hole" in diamond code



Number of possibilities	4	+	4	+	6	+	6	= 20.

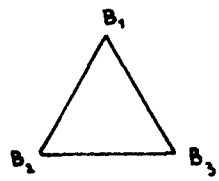
This code has been called the "diamond code" depending on the form of the figures, and since the base sequence is "read" in the following way:

$$B_1B_2B_3B_4B_5B_6B_7B_8 \cdots$$

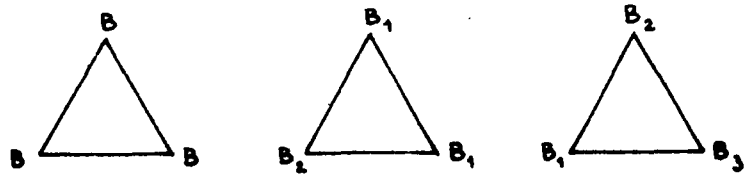
it is characterized as an "overlapping triple code". Gamow realized that these overlappings, i.e. the fact that two neighbouring holes have two common nucleotides, would have important consequences and lead to a partial correlation between neighbouring amino-acids in the proteins. If $B_1B_2B_3$ codes the amino acid α and $B_2B_3B_4$ the amino acid β, the

sequence $B_1B_2B_3B_4$ would code the dipeptide $\alpha\beta$. However, since there are $4^4 = 256$ possible quadruples $B_1B_2B_3B_4$ but $20^2 = 400$ dipeptides $\alpha\beta$, it is clear that there would be many dipeptides which could never occur.

Another overlapping code suggested by Gamow [19] et.al. was the "triangular code" based on the idea, that the triplet $B_1B_2B_3$ may be equivalent with all other triplets obtained by rotation and/or reflexion. Even this code leads to exactly 20 independent triplets as follows:



Gamow "hole" in triangular code



Number of possibilities:	4	+	12	+	4	= 20.

During the years following Gamow's hypothesis, there was an intense research as to overlapping codes [19] and the question of correlation in dipeptides. However, no experimental evidence for such a correlation could be found [19], and finally Brenner [20] showed that there seemed to be a sufficiently large number of dipeptides in nature to prove the impossibility of all overlapping triplet codes.

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19) G. Gamow and M. Ycas, Proc. Nat. Acad. Sci. U.S. 41, 1011 (1955); G. Gamow, A. Rich, and M. Ycas, Adv. Biol. and Med. Phys. 4, 23 (Academic Press 1956).

20) S. Brenner, Proc. Acad. Sci. U.S. 43, 687 (1957).

In 1957, Crick [21] et. al. introduced another interesting development through the "comma-less code" meaning that there would only be

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21) F.H.C. Crick, J.S. Griffith, and L.E. Orgel, Proc. Nat. Acad. Sci. U.S. 43, 416 (1957).

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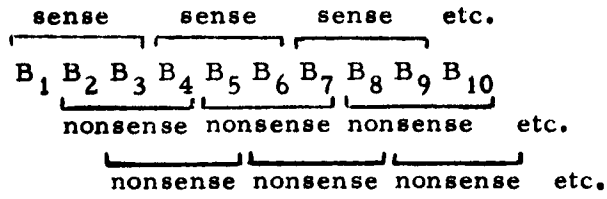
one division of the base message into triples which had sense, whereas all other divisions would be sense-less:



On the basis of this simple rule, they could show that there existed such "comma-less" codes. If the triple BBB is assumed to code the amino acid α, the sequence BBB BBB would code the dipeptide $\alpha\alpha$ but would also contain two more triples which ought to be nonsense; hence the entire triple should be rejected. This leaves 64 - 4 = 60 triples at our disposal. Let us then consider a sense triplet $B_1B_2B_3$ which is assumed to code the amino acid β. The sequence $B_1B_2B_3B_1B_2B_3$ codes the dipeptide $\beta\beta$ and contains the sense-less triples $B_2B_3B_1$ and $B_3B_1B_2$, i.e. the triples obtained from the original one through cyclic permutations. Since 60:3 = 20, it is clear that the maximum number of "sense triplets" cannot exceed the magic number 20. Crick et. al. show by an example that there exist actually exactly 20 sense triplets:

Type I	$1\,2\,\frac{1}{2}$	,	$\frac{1}{2}\,3\,\frac{1}{2}$	,	$\frac{1}{2}\,4\,\frac{1}{2}$				
			$\quad 3$		$\quad 3$		$\quad 3$		
Number of possibilities	2	+	6	+	12	=	20	.	

In each group with a fixed middle figure, one may take all combinations of the first and the last figures to form sense-triples. The "comma-less" code has a great physical advantage, since it implies that only "sense-

triples" can catch an amino-acid which comes then from the very beginning into the correct place.

All possible types of comma-less codes have now been systematized[22]

22) H. Freudenthal, Koninkl. Ned. Akad. Wetenschap Proc. A61, 253 (1958); S.W. Golomb, L.R. Welch, and M. Delbrück, Biol. medd. Dan. Vid. Selsk. 23, 9 (1958).

and four more types should be mentioned:

Type II	2 1 1 ,	1 2 2 ,	$\begin{matrix}1&&\\&2&1\\3&&2\\&&3\end{matrix}$,	$\begin{matrix}1&&&1\\&2&&2\\2&&4&3\\3&&&4\end{matrix}$
Type III	$\begin{matrix}1&&1\\3&2&2\end{matrix}$,	$\begin{matrix}1&&1\\2&3&3\end{matrix}$,	$\begin{matrix}1&&&1\\&2&&2\\2&&4&3\\3&&&4\end{matrix}$
Type IV	$\begin{matrix}1&2&1\\&&2\end{matrix}$,	$\begin{matrix}1&&1\\2&3&2\\4&&3\end{matrix}$,	$\begin{matrix}1&&1\\2&4&2\\3&&4\end{matrix}$
Type V	1 2 1 ,	2 1 1 ,	$\begin{matrix}1&&1\\2&3&2\\4&&3\end{matrix}$,	$\begin{matrix}1&&1\\2&4&2\\3&&4\end{matrix}$

With these types, the possibilities for constructing comma-less codes are extinguished.

The coding problem is still not solved, and there remains the important question whether there actually exists a "universal code", or whether the code could be different for various species. Using experimental evidence from amino-acid sequences and properties of mutants, several authors have contributed to the solution of the problem [23]. By now

23) C. Levinthal, Revs. Modern Phys. 31, 249 (1959); M. Ycas, Nature 188, 209 (1960); C.R. Woese, Nature 190, 697 (1961); Biochem. Biophys. Res. Commun. 5, 88 (1961); G. Zubay and H. Quastler, Proc. Nat. Acad. Sci. U.S. 48, 461 (1962); R.B. Roberts, ibid. 48, 897 (1962); S. Benzer and S.P. Champe, ibid. 48, 1114 (1962).

even the comma-less codes seem to be abandoned, and the situation has been summarized by Crick [24] et. al. in the following way: the code

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24) F.H.C. Crick, L. Barnett, S. Brenner, and R.J. Watts-Tobin, Nature 192, 1227 (1961); F.H.C. Crick, Uppsala Lectures 1962.

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seems to be a degenerate non-overlapping triplet code which is read from a fixed starting point without special "commas". The word "degenerate" means here that there are several triplets which may code one and the same amino acid.

Recently the entire coding-problem has been moved closer to a solution through a remarkable development in biochemistry. Extending the techniques developed by Kornberg and by Ochoa for the synthesis of polynucleotides, Nirenberg and Matthaei [25] succeeded in using a simple

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25) M. W. Nirenberg and J.H. Matthaei, Proc. Nat. Acad. Sci. U.S. 47, 1588 (1961); J.F. Speyer, P. Lengyel, C. Basilio, and S. Ochoa, ibid. 48, 63 (1962); W.B. Wood and P. Berg, ibid. 48, 94,(1962).

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polynucleotide of the type UUUUU ... as a template in the biosynthesis of polypeptides. Since the result was a polyphenylalanine peptide, it seems hence as if the group UUU would code phenylalanine. Further studies of a polynucleotide containing the bases U and G in the ratio 5:1 showed that the corresponding polypeptide, in addition to phenylalanine, contains the amino acids leucine, valine, glycine, and tryptophane. The proportions are such that it seems likely that the coding letters for leucine and valine are UUG and for glycine and tryptophane UGG. The method has presently the difficulty that, in a "mixed" polynucleotide, one does not know the exact order between the bases, so that one has to work with an assumption of random distribution. The nearest future will show whether one can obtain a full solution of the coding problem in this way, and whether there exists a universal code.

Viruses. - The study of viruses started with the discovery that certain diseases could be produced by particles which would pass through filters stopping bacteria and which hence would have much smaller dimensions. After several decades of intense research, we know today that a virus consists essentially of a DNA-molecule or RNA-molecule in a protein "overcoat". When a virus approaches a cell, it will throw off its protein overcoat, and the DNA- or RNA-molecule will enter through the cell membrane. The virus DNA- or RNA-molecule will then take over the control of the metabolism of the "host" cell, and it will start replicating itself until most of the cell material is exhausted. The new DNA- or RNA-molecules will then be wrapped into protein overcoats so that, when the cell membrane bursts, they are ready to enter the invironment and approach new host cells.

One distinguishes between four types of viruses: bacterial, animal, plant, and insect viruses, of which the first type (the "bacteriophages") has been of particular importance in the study of DNA and RNA as hereditary substances. One has found that the single-stranded virus RNA-molecule has the same power of replication as the double-stranded DNA-molecule, and that, in exceptional cases, there seems to exist also a single-stranded DNA-molecule. However, in all cases, one believes that the replication uses a template-mechanism built on Watson-Crick's complementarity idea [26].

Whether the viruses are to be considered as "living" or "dead" matter is ultimately a question of semantics. A virus may be considered as a giant molecule in a stationary state which may remain the same for a very long time and has all the characteristics of dead organic matter. However, when the virus is brought into interaction with a host cell, it starts replicating itself and shows thus the most fundamental property of "living" matter.

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26) A. Hershey and M. Chase, J. Gen. Physiol. 36, 39 (1952); E. Pollard, "The Physics of Viruses" (Academic Press, New York 1953); H.B. Fraenkel-Conrat, B.A. Singer, and R.C. Williams, "Chemical Basis of Heredity", 501 (Edited by W.D. McElroy and B. Glass, Johns Hopkins Press, Baltimore 1957); H. Fraenkel-Conrat, Harvey Lectures 53, 56 (1959); E. Burnet and W.H. Stanley, "The Viruses" (Academic Press, New York 1959).

4. PROPERTIES OF THE HYDROGEN BOND

Since the Watson-Crick model essentially utilizes the hydrogen bond in the definition of the complementarity between the nucleotide bases, it may be worthwhile to study the properties of this bond in greater detail.

Chemical experience has shown that a hydrogen atom attached to an electronegative atom in a molecule may also be attracted to another electronegative atom in a different molecule, in this way leading to a "hydrogen bond" between the two molecules. Sometimes there is also an internal hydrogen bond between two electronegative atoms within the same molecule. The atoms which form the strongest hydrogen bonds are in order after decreasing strength: fluorine, oxygen, and nitrogen, whereas weak bonds are formed by chlorine and carbon. Experimentally the properties of the hydrogen bonds have been studied extensively and, for a survey, we would like to refer to Pimentel and McClellan [27] and to the proceedings [28] from the 1957 conference.

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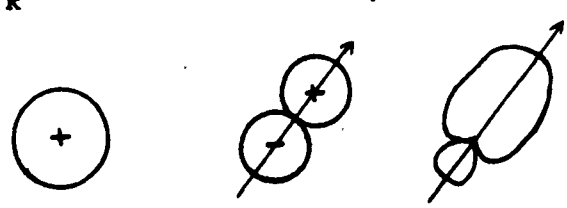
27) G.C. Pimentel and A.L. McClellan, "The Hydrogen Bond" (Freeman and Co., San Francisco 1960).

28) "Hydrogen Bonding", Proc. Int. Symp. Ljubljana 1957 (Editor D. Hadzi, Pergamon Press, London 1959).

Electron-Proton Formulation of the Hydrogen Bonding . - In order to investigate the properties of the hydrogen bond, one has to understand the electronic structure of the atoms involved. According to the idea of hybridization introduced by Pauling and Slater in 1932, the orbitals of the valence electrons are superimposed or hybridized to form orbitals having a particularly high electron density in specific directions corresponding to directed valency. By superposition of an s-orbital and a p_k-orbital, one obtains a hybrid:



s p_k h

$$h = \alpha s + \beta p_k \, .$$

$$(\alpha > 0, \ \beta > 0)$$

which has its maximum density in the k-direction. The normalization condition $\langle s|s\rangle = \langle p_k|p_k\rangle = \langle h|h\rangle = 1$ gives $\alpha^2 + \beta^2 = 1$. The ratio $n = \beta^2/\alpha^2$ indicates the amount of p-character relative to the amount of s-character, and the hybrid is conventionally denoted by the symbol sp^n, where n does not necessarily have to be an integer.

It there are two hybrids, h_1 and h_2, which are orthogonal in Hilbert space so that $\langle h_1|h_2\rangle = 0$, one has

$$\langle h_1|h_2\rangle = \alpha_1\alpha_2 + \beta_1\beta_2\langle p_1|p_2\rangle = 0 .$$

Since $\langle p_1|p_2\rangle = \cos\theta_{12}$ gives the cosine for the geometrical angle θ_{12} between the two hybrids, this leads to

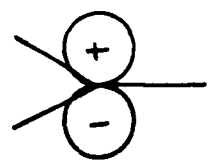
$$\cos\theta_{12} = -\frac{1}{\sqrt{n_1 n_2}} ,$$

which relation gives the connection between the geometrical structure and the amount of hybridization.

If there are four mutually orthogonal hybrids sp^{n_1}, sp^{n_2}, sp^{n_3}, and sp^{n_4}, the total amount of s- and p-character has to be used up which leads to the auxiliary condition:

$$\frac{1}{n_1+1} + \frac{1}{n_2+1} + \frac{1}{n_3+1} + \frac{1}{n_4+1} = 1 .$$

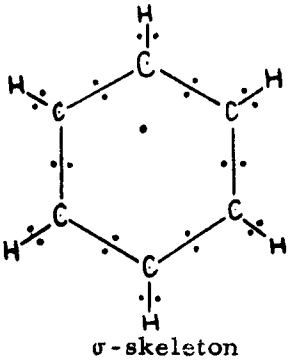
The necessary and sufficient condition that three hybrids should be in the same plane is simply



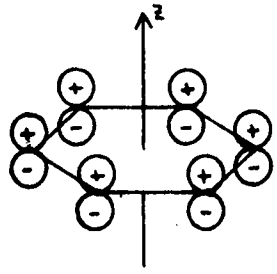
$$\frac{1}{n_1+1} + \frac{1}{n_2+1} + \frac{1}{n_3+1} = 1 ,$$

and it is then easily seen that the fourth hybrid must be a pure p-orbital perpendicular to the plane. The coplanar hybrids are said to form the σ-part of electronic structure, whereas the p-orbital forms the π-part. The σ- and π-orbitals are characterized by being symmetric and antisymmetric, respectively, with respect to reflexions in the plane.

The most symmetric planar structure is the benzene molecule C_6H_6, where the angles are 120^o and the carbon atoms have sp^2-hybridization. Three valence electrons from each carbon atom participate in the single bonds in the σ-skeleton, whereas the fourth valence electron enters one of the molecular orbitals formed by linear superposition of the $2p_z$-orbitals of the individual carbon atoms and contributes to the π-electron cloud.

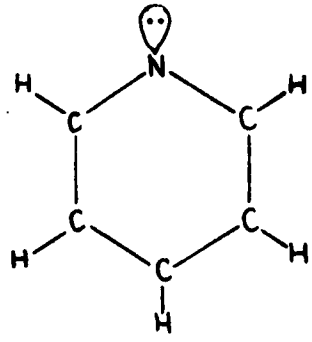


σ-skeleton

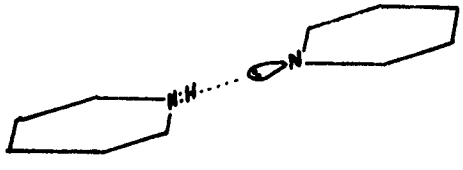


π-electron cloud

Let us now assume that we could carry out a thought-experiment consisting of dropping one of the protons around the ring into one of the carbon nuclei giving rise to a nitrogen nucleus. This would lead to the formation of a pyridine molecule characterized by having an electron lone-pair sitting in a sp^2-hybrid on the nitrogen atom. The number of π-electrons will remain unchanged and equal to 6. It is clear that the extra positive charge on the N-atom will attract the mobile π-electrons and serve as an "electron trap". Even the lone pair will be influenced, but the main structure will still be two electrons in a σ-orbital pointing far out in space from the ring. This lone pair will attract every proton (or positive group) in the neighbourhood, and this tendency of pyridine to try to catch a proton and become a pyridinium ion $C_5NH_6^+$ gives it the characteristic "base" character.



If there are several molecules having such electron lone-pairs in a system, there may be a competition to catch the protons in the environment which leads to the formation of the abovementioned hydrogen bonds. In this type of formulation, a hydrogen bond is characterized as a proton shared between two electron lone pairs.

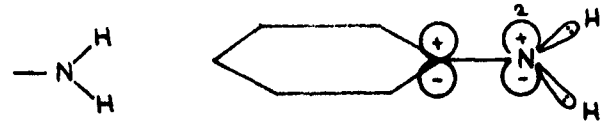


The figures below indicate the approximate electronic structure of nitrogen and oxygen atoms in some groups commonly occurring in conjugated systems:

Nitrogen in

1) ring

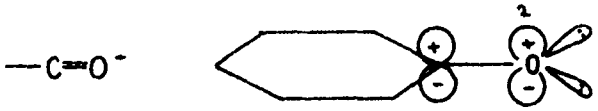
2) amino group



3) imine group

Oxygen in

1) keto group



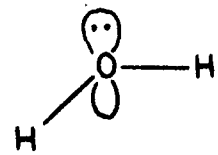
2) enol group

The following table gives a survey of the electron distribution of C, N, O, and F commonly occurring in these groups:

Atom	Valence electrons	Group	σ-electrons		π electrons
			Single bonds	In lone pairs	
C	4	Ring	3	-	1
N	5	Ring	2	-	1
	5	Amino	3	-	2
N^-	6	Imine	2	2	2
O	6	Enol	2	2	2
O^-	7	Keto	1	2 + 2	2
F	7		1	2 + 2	2

The number in the last column gives the number of π-electrons contributed to the mobile electrons. However, since part of these electrons in attached groups migrate into the ring, the actual π-charge is always less than 2. The table gives an idea why the strength of the hydrogen bond goes F > O > N >> C.

A substance which is highly characterized by hydrogen bonding is water, where the oxygen atom has at least one electron lone-pair easily available, and the water molecule has then the tendency to try to catch a proton and form the hydronium ion H_3O^+. This proton may be taken from another water molecule, which then forms the hydroxyl ion OH^- with two electron lone pairs easily available. The competition to catch protons between the water molecules leads to the effect of hydrogen bonding which is highly essential for the properties of the fluid [29].



29) J. Lennard-Jones and J.A. Pople, Proc. Roy. Soc. (London) A205, 155 (1951); J.A. Pople, ibid. A205, 163 (1951).

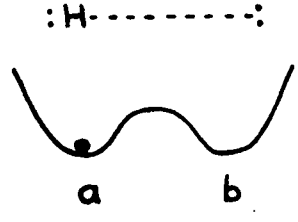
In each hydrogen bond, the proton has two equilibrium positions - one close to each one of the two electron lone-pairs involved:

If these equilibrium positions are equivalent, one can expect that, under certain conditions, the proton may jump from one position to another. Since such a jump will influence the gross electric neutrality of the entire environment, it may induce other proton jumps so that the final effect will be a collective phenomenon. This process in the ice crystal has been studied by Pauling [30], and he shows that it has important consequences for the residual entropy of ice.

30) L. Pauling, "Nature of the Chemical Bond", (Cornell University Press, Ithaca 1939); see p. 464 in third edition (1960).

It is evident that the "proton exchange" which occurs in connection with the hydrogen bonding is of great importance in the study of the tautomeric forms of the molecules involved, and that this exchange may be the main mechanism for approaching the so-called "tautomeric equilibrium". When Knorr in 1911 succeeded in separating the keto-and enol-forms of ethyl acetoacetate from each other, it appeared that, at room temperature, it would take weeks until the pure forms had reached the tautomeric equilibrium again. This time may be shortened, if there are additional protons available. However, if proton exchange and shifts between different tautomeric forms seem to be general features of systems having hydrogen bonds, one may wonder what precautions have to be taken to preserve a "proton-code" in a stationary form for thousands of years, as in the DNA-molecule in the Watson-Crick model. Apparently nature has succeeded very well.

Quantum Theory of the Hydrogen Bond; Tunnel Effect. - The question of the motion of a proton in a hydrogen bond is, in a first rough approximation, a one-particle problem involving a fixed outer potential. Each electron-pair attracts the proton, and this attraction may be represented by a double well. Since there are two electron-pairs involved, the total effect is hence represented by a "double-well potential" of the form:



The problem is then to solve the time-dependent Schrödinger equation:

$$H_{op}\,\Psi = -\frac{h}{2\pi i}\frac{\partial \Psi}{\partial t} \qquad (3)$$

where H_{op} is the conventional Hamiltonian operator. If the initial situation at time $t = 0$ is given by the wave function Ψ_0, the time-dependence is described by the symbolic formula:

$$\Psi(t) = \exp\left(-\frac{2\pi i}{h} H_{op}\, t\right)\Psi_0 . \qquad (4)$$

This solution may be written in a more convenient form by introducing the "orthonormal" set $\{\Phi_n\}$ of solutions to the eigenvalue problem $H_{op}\Phi_n = E_n\Phi_n$ having the eigenvalues E_n and eigenfunctions Φ_n under certain boundary conditions. Assuming that the set is complete so that there is a "closure" or resolution of the identity $1 = \sum_n |\Phi_n\rangle\langle\Phi_n|$, one obtains

$$\Psi(t) = \sum_n \exp(-\tfrac{2\pi i}{h} E_n t)\, \Phi_n \langle\Phi_n|\Psi_0\rangle , \tag{5}$$

which form is known as the "expansion into stationary states".

Let us start by considering the case when the double-well potential is symmetric. In this case, the reflexion in the mid-point plane is a normal constant of motion [31] with the eigenvalues ± 1, and there are

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31) See e.g. P.O. Löwdin, Revs. Modern Phys. 34, 520 (1962).

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two types of solutions which are "gerade" g or "ungerade" u with respect to this operation. Let us denote proton orbitals associated with the two potential minima by a and b, respectively. Let us further assume that the experimental situation is such that, at $t = 0$, the proton is fully in one of these positions, say $\Psi_0 = a$. Since

$$a = \tfrac{1}{2}(a+b) + \tfrac{1}{2}(a-b) \tag{6}$$

gives the resolution of the initial state into symmetry components [31], one obtains according to (5), after making the simplifying assumption that there is only one state of each symmetry involved, that

$$\begin{aligned}\Psi(t) &= \tfrac{1}{2}(a+b)\exp(-\tfrac{2\pi i}{h}E_g t) + \tfrac{1}{2}(a-b)\exp(-\tfrac{2\pi i}{h}E_u t) = \\ &= \left[\tfrac{1}{2}(a+b) + \tfrac{1}{2}(a-b)e^{-2\pi i\nu t}\right]\exp(-\tfrac{2\pi i}{h}E_g t),\end{aligned} \tag{7}$$

where $\nu = (E_u - E_g)/h$ is the Bohr frequency associated with the two levels E_u and E_g. Introducing the period $T = 1/\nu$, one obtains for the proton distribution:

$$|\Psi(t)|^2 = \left|\tfrac{1}{2}(a+b) + \tfrac{1}{2}(a-b)\exp(-2\pi i t/T)\right|^2 \tag{8}$$

showing that, at the times $t = 0, T, 2T, \ldots$, the proton is in position a whereas, at the times $t = T/2, 3T/2, 5T/2, \ldots$, the proton is in position b. Hence, we have proven that, if the proton is originally in one of the classical "equilibrium positions", it will oscillate between the two potential minima with the frequency $\nu = 1/T$. The "proton jumping" is thus a typical quantum-mechanical phenomenon.

Using a technique previously developed [31], one finds easily the following expressions for the energies involved:

$$E_g = \frac{\langle a|H|a\rangle + \langle a|H|b\rangle}{\langle a|a\rangle + \langle a|b\rangle} , \tag{9}$$

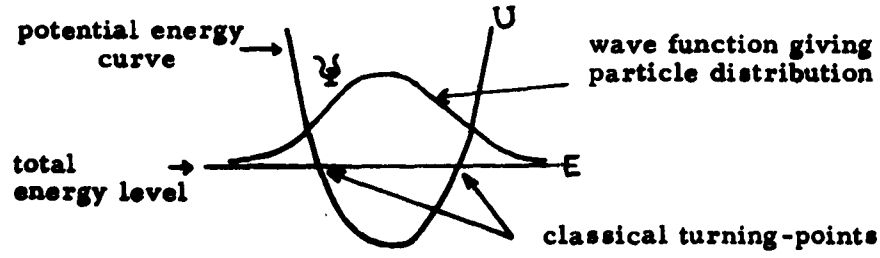
$$E_u = \frac{\langle a|H|a\rangle - \langle a|H|b\rangle}{\langle a|a\rangle - \langle a|b\rangle} . \tag{10}$$

Introducing the normalization $\langle a|a\rangle = 1$, this gives for the proton exchange frequency:

$$\nu = 2h^{-1} \frac{\langle a|H|a\rangle\langle a|b\rangle - \langle a|H|b\rangle}{1 - \langle a|b\rangle^2} , \tag{11}$$

which relation shows that the exchange depends essentially on the overlap between the proton orbitals a and b which results when the two isolated potential minima are brought together to a double-well potential. One could then ask how such an overlap could occur at all.

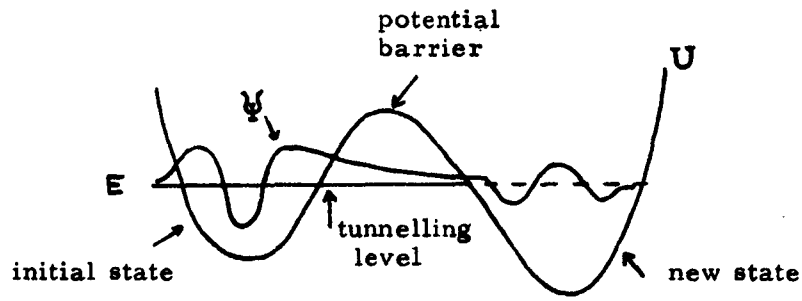
Already the first study of the harmonic oscillator according to modern quantum theory showed that the particle involved could exist outside the classical "turning points":



This depends on the fact that the quantities kinetic energy and potential energy are not simultaneously measurable [32]. The phenomenon implies

32) For a detailed discussion, see e.g. H. Kramers, "Quantum Mechanics" (North Holland Publishing Co., Amsterdam 1957), p. 60-61.

that, if the potential energy curve shows two classically permitted intervals separated by a forbidden region, a quantum-mechanical particle may leak through the potential barrier from one "permitted" state to another. This phenomenon is known as the "tunnel effect":



The effect was first used by Gamow [33] to explain the general phenomenon of radioactivity, which implies a transition from a bound state to a state in the continuum with a free particle emitted. The fact that the radioactive half-life times range from small fractions of seconds to thousands of years shows that tunnelling probabilities can take values of all orders of magnitude. In molecular spectroscopy, the tunnel effect is quite well-known as causing the phenomenon of predissociation [34]. In solid-state physics, the effect has been utilized for the technical construction of certain types of semi-conductors known as tunnelling-diodes [35]. There seems also to be good reasons for believing that corrosion may be due to loss of order through particle-tunnelling.

33) G. Gamow, Z. Physik 51, 204 (1928); ibid. 52, 510 (1928). R.W. Gurney and E.U. Condon, Phys. Rev. 33, 127 (1929).

34) See e.g. G. Herzberg, "Spectra of Diatomic Molecules" (D. van Nostrand, Princeton 1950), particularly p. 409 in 2nd ed.; L.D. Landau and E.M. Lifshitz, "Quantum Mechanics" (Pergamon Press, London 1958), p. 305.

35) T. Yajima, L. Esaki, J. Phys. Soc. Japan 13, 1281 (1958); L. Esaki, "Solid-State Physics in Electronics and Telecommunications", 1, 514 (Academic Press, New York 1960).

In ordinary chemistry, the tunnel effect has so far been of smaller importance. In the theory of chemical kinetics, one would usually consider only processes which would have sufficient energy to take the components above the potential barrier between the two states involved, and the effect of tunnelling is usually so small that it can be neglected. However, in certain biochemical processes where one has the effect of "biological amplification", it could very well happen that even the chemical effects of tunnelling may show up, as we shall see below.

Let us now return to the hydrogen bond and the double-well potential. It is evident that it is the fact that a proton can move even in classically forbidden regions which gives rise to an overlap between the orbitals a and b associated with the different equilibrium positions, and the oscillation of the proton may thus be considered as an example of the tunnel-effect. It should be observed that the oscillating proton is not in a stationary state; such states are instead represented by the simple wave functions $\frac{1}{2}(a + b)$ and $\frac{1}{2}(a - b)$ corresponding to a 50 - 50 o/o distribution of the proton over the two positions.

We have here discussed essentially the symmetric potential, but the general arguments may be extended also to the asymmetric double--well potential. The tunnel-effect in quantum theory is conventionally treated by the so-called WKB-method and various refinements of this approach[36]. For some recent developments in the theory of the hydrogen bond, we would like to refer to the 1957 symposium[37] and to the works by Hofacker[38], Fischer-Hjalmars[39] and Grahn[39].

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36) See e.g. N.F. Mott and I.N. Sneddon, "Wave Mechanics and its Applications" (Clarendon Press, Oxford 1948), p. 15; L.D. Landau and E.M. Lifshitz, "Quantum Mechanics" (Pergamon Press, London 1958), p. 171.

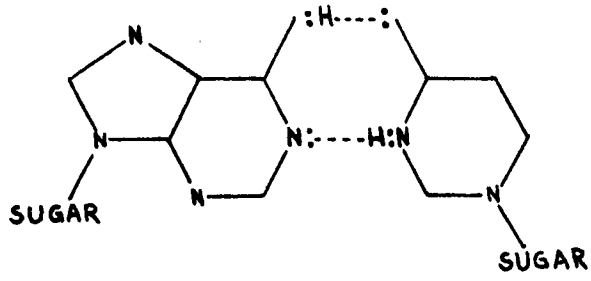
37) C.A. Coulson, Proc. Int. Symposium on Hydrogen Bonding, Ljubljana 1957 (Editor D. Hadzi, Pergamon Press, London 1959), p. 339; E.R. Lippincott, J.N. Finch, and R. Schroeder, ibid., p. 361; L. Hofacker, ibid., p. 375; N.D. Sokolov, ibid., p. 385; M. Davies, ibid., p. 393; and several other contributions. See also the survey in L.E. Orgel, Revs. Modern Phys. 31, 100 (1959).

38) L. Hofacker, Z. Naturforsch. 13a, 1044 (1958).

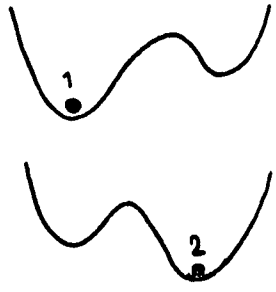
39) I. Fischer-Hjalmars and R. Grahn, Acta Chem. Scand. 12, 584 (1958); R. Grahn, Arkiv Fysik 15, 257 (1959); 19, 147 (1961); 21, 1 (1962); 21, 13 (1962); 21, 81 (1962).

5. QUANTUM THEORY OF DNA

Proton Tunnelling in DNA. - The hydrogen bonds play a fundamental role in the complementarity concept developed by Watson and Crick in their stereomodel of DNA. One can condense the essential features of the base pairing described in Fig. 5 in the schematic diagram:



There are at least two hydrogen bonds involved, and the problem of the genetic code is hence concerned with the question of the motion and stability of two protons in a four-well potential:



upper hydrogen bond

lower hydrogen bond

i.e. one has to treat a quantum-mechanical two-body problem. Since the movements of the protons will further polarize the electron clouds and hence also change the potentials, a complete solution will undoubtedly be rather complicated. For the sake of simplicity, we will first consider the two double-well potentials as fixed.

Since it is essential for the entire Watson-Crick model that the protons remain in their "normal" positions in the base pairs in order to represent a pure genetic message, one has to assume that the double--well potentials are highly asymmetric. A fundamental quantum-mechanical problem in the study of DNA is hence to investigate whether this is actually the case. On this basis, one could perhaps understand why nature has chosen each base pair to consist of different partners - one purine and

one pyrimidine base. A detailed study of this problem including also the symmetric combinations (purine-purine and pyrimidine-pyrimidine) would definitely be of some interest.

However, even if the double-well potential in each hydrogen bond is highly asymmetric, one can expect that there will always be a small probability for proton tunnelling through the potential barrier in the middle of the bond. Two cases have to be distinguished:

a) Bases with equal charge. In this case the tunnelling of one proton in one direction will very likely induce a tunnelling of the other proton in the reverse direction to keep balance between the gross electric charges, so that

This simultaneous proton tunnelling implies the base transitions:

$$A - T \longrightarrow A^* - T^*, \qquad G - C \longrightarrow G^* - C^*,$$

which leads to the production of pairs of tautomeric bases. If the hydrogen bonds get released in this position, the tautomeric forms will lead to errors in the next replication, i.e. to mutations. In this connection, it should be observed that the tunnelling probabilities depend not only on the base pair involved but also on the electrostatic environment, the neighbouring base pairs etc., which may explain the occurrence of "hot spots". The effects will be discussed in greater detail in Sec. 7.

A quantum-mechanical analysis of the shape of the "wave packet" associated with the proton shows that, even in the ground state of the molecule, the genetic message in DNA can never be entirely "pure", since the wave function is such that there is always a small probability that the proton occurs in the "wrong" position. In this ground state, the proton distribution is stationary without any oscillations. However, if one tries to refine the code by condensing the wave packet in order to place it within the limits of one of the potential wells alone, one is actually raising the energy, and the proton starts oscillating between the two classical

equilibrium positions. It is hence clear that, irrespective of whether one considers a stationary state or a time-dependent situation, there does not exist a pure genetic message in the form of a completely stable "proton code" in the sense of Watson and Crick.

b) Bases with unequal charge. If one of the bases in a pair has obtained an extra charge, the shape of the double-well potential is changed and the probability for a proton tunnelling is often greatly increased. Under these conditions, the proton transfer goes essentially in one direction:

This leads to transitions of the type $A\text{-}T \rightarrow A^+\text{-}T^-$ or $A^-\text{-}T^+$ and the type $G\text{-}C \rightarrow G^+\text{-}C^-$ or $G^-\text{-}C^+$. In this case one obtains two ionic tautomeric forms which otherwise do not appear in the Watson-Crick model and which can be expected to cause mutations of a somewhat different type; see further Sec. 7.

One may wonder under what conditions the bases within a pair get unequal charges. Through electronic donor-acceptor reactions with other molecules, an electron may be added (or removed) to the π-electron cloud of one of the bases. One electron is further often removed from the π-part of one of the bases through the (direct or indirect) effect of ionizing radiation. An important process is probably the addition of a proton to one of the purine bases through bonding to one of the extra electron lone-pairs available at the N_3- and N_7-positions, which means that proper attention should be given also proton reactions. It should finally be mentioned that the double-well potential may be disturbed through additional electrostatic potentials from outer sources, dipole double-layers, etc. The dimensions may also be changed through external pressure, ultra-sound waves etc. Other interesting problems to be studied include the effect of radiation in resonance with the proton tunnelling frequency, as well as the effect of strong magnetic fields on the proton spins. We will return to some of these problems in Sec. 7.

It may seem very tempting to try to study the phenomenon of "proton

exchange" experimentally by means of "tagged" protons in the form of deuterium D and tritium T . So far one has been rather successful in producing "deuterated" organisms, and transformation experiments could be carried out. However, in interpreting experiments of this type, one has to remember that the mass of the particles involved has been changed and considerably increased which will in turn lower the tunnelling probability.

Electronic Structure of DNA. - Since even the finer details of the electrostatic potentials acting on the two protons may be of importance in connection with the tunnelling effect, it is highly desirable to determine the electronic structure of DNA with a great deal of accuracy. Since the knowledge of this electronic structure is of essential importance also in many other connections, a great deal of effort should be devoted to improving the methods available and the computational technique.

The electronic structure consists of the σ-skeleton associated with the single bonds and the π-electron cloud corresponding to the conventional double bonds. So far most of the attention has been devoted to the mobile π-electrons and their biochemical importance. A first estimate of the charge and bond orders of the nucleotide bases has been made by the Pullmans [40] by means of the conventional Hückel-approximation, and this approach has also been used by Ladik [41] and by Ladik and Appel [42].

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40) A. Pullman and B. Pullman, Nature 189, 725 (1961).

41) J. Ladik, Acta Phys. Hung. 11, 229 (1960).

42) J. Ladik and K. Appel, Technical Notes 78 and 79, Uppsala Quantum Chemistry Group (1962).

The "Hückel-scheme" developed by Hückel in the beginning of the 1930's is a special form of the molecular-orbital method applied to aromatic compounds and conjugated systems in general. It is assumed that each π-electron moves in the average field coming from the nuclei, the σ-skeleton, and all the other π-electrons and obeys a one-electron Schrödinger equation of the form:

$$H_{eff}\,\psi_k = \epsilon_k \psi_k \quad , \qquad (12)$$

where H_{eff} is the so-called effective Hamiltonian. By introducing the atomic p_z-orbitals as a basis $\{\phi_\mu\}$ and assuming the existence of the expansion $\psi_k = \sum_\nu \phi_\nu c_{\nu k}$, one obtains $\langle \phi_\mu | H_{eff}\psi_k - \epsilon_k\psi_k \rangle = \sum_\nu \langle \phi_\mu | H_{eff} - \epsilon_k | \phi_\nu \rangle c_{\nu k} = 0$. Introducing the matrix elements of the Hamiltonian, $H_{\mu\nu} = \langle \phi_\mu | H_{eff} | \phi_\nu \rangle$ with the special notations

$$\alpha_\mu = \langle \phi_\mu | H_{eff} | \phi_\mu \rangle , \qquad \beta_{\mu\nu} = \langle \phi_\mu | H_{eff} | \phi_\nu \rangle , \quad \mu \neq \nu , \tag{13}$$

and the metric matrix $\Delta_{\mu\nu} = \langle \phi_\mu | \phi_\nu \rangle$, one obtains the system of linear equations

$$\sum_\nu (H_{\mu\nu} - \epsilon \Delta_{\mu\nu}) c_{\nu k} = 0 , \tag{14}$$

with the secular equation $\det \{ H_{\mu\nu} - \epsilon \Delta_{\mu\nu} \} = 0$ determining the orbital energies ϵ_k. After determining the coefficients $c_{\nu k}$, one can calculate the charge order q_μ of atom μ and the bond order $p_{\mu\nu}$ of the bond μ-ν by the relations:

$$q_\mu = \sum_k c_{\mu k} c^\dagger_{k\mu} , \qquad p_{\mu\nu} = \tfrac{1}{2} \sum_k (c_{\mu k} c^\dagger_{k\nu} + c_{\nu k} c^\dagger_{k\mu}) , \tag{15}$$

where k is summed over all occupied orbitals ψ_k, taking doubly occupied orbitals twice. In the standard Hückel approximation, one considers only interaction between nearest neighbours, and the matrix elements α and β are treated as semi-empirical parameters; in heterocyclics, the differences in the α_μ-values are further related to the electronegativity differences between the atoms involved.

Experiences from the quantum-mechanical study of many types of conjugated systems indicate, however, that, in order to get a full and reliable understanding of the electronic structure of such systems in their ground state and excited states, it is necessary to go far beyond the Hückel-approximation. Since this scheme is based essentially on the independent-particle-model, it is particularly important to have the electronic correlation [43] properly included.

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43) See e.g. P.O. Löwdin, Adv. Chem. Phys. 2, 207 (Editor: I. Prigogine, Interscience, New York 1959).

The Hückel-scheme has recently been refined by extending the so-called self-consistent-field ideas to exact form. This has been achieved by considering a formal solution to the many-electron Schrödinger equation based on a simple partitioning technique equivalent to infinite-order perturbation theory. The reaction operator obtained in this way is utilized to construct an exact self-consistent-field scheme [44] which is a direct generalization of the Hückel method. The scheme may be used for ab-initio calculations by means of electronic computers but seems still more appropriate for semi-empirical discussions and for the study of fundamental concepts. This approach has so far been used to investigate the problem of the change of bond orders and bond lengths under addition and substitution, and to study the connection between the Hückel parameters and Pauling's concept of electronegativity [45].

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44) P.O. Löwdin, J. Math. Phys. 3, 969, ... (1962).

45) P.O. Löwdin, Technical Note 83, Uppsala Quantum Chemistry Group, 1962.

Symmetry properties and particularly the total spin could further be conveniently treated by the projection operator technique [46]. In addition to the Hückel scheme, the method using "different orbitals for different spins" could also be utilized for treating the correlation problem, particularly in the alternant conjugated systems involved [47]. Full attention should be paid to the non-orthogonality problem [48].

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46) P.O. Löwdin, Revs. Modern Phys. 34, 520 (1962).

47) P.O. Löwdin, Symposium on Molecular Physics, Nikko, Japan (1953), 13; Phys. Rev. 97, 1509 (1955); Adv. Chem. Phys. 2, 207 (1959); Ann. Rev. Phys. Chem. 11, 107 (1960); R. Pauncz, J. de Heer and P.O. Löwdin, J. Chem. Phys. 36, 2247, 2257 (1962); P.O. Löwdin, J. Appl. Phys. 33, 251 (1962).

48) P.O. Löwdin, J. Chem. Phys. 18, 365 (1950); Adv. Phys. 5, 1 (1956), p. 49-56.

Such an investigation of the detailed electronic structure of DNA should start by considering the single bases, then base pairs, then a series of base pairs, etc., until one obtains a reasonable model of DNA. One can utilize the fact that the electronic structure of the bases involved remains rather stable and that the actual changes may be calculated by means of the theory for "localized perturbations" [49]. In addition to the π-electron system of the bases, a great deal of attention should be devoted to the σ-electron frame work, and particularly the character of the "lone pairs" should be studied in full detail. Work along these lines is now in progress in Uppsala.

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49) P.O. Löwdin, Technical Note 65, Uppsala Quantum Chemistry Group 1962; M.A. Ali and R.F. Wood, Technical Note 75, Uppsala Quantum Chemistry Group 1962.

Detailed Structure of the Hydrogen Bonds. - It is clear that, in order to obtain the full details of the protonic structure of the hydrogen bonds in DNA, it may be necessary to use rather refined quantum-mechanical methods. In a first approximation, it may be feasible to separate the motions of protons from the motions of the electrons, and to consider the behaviour of the protons in the fixed average electrostatic potential arising from the remaining part of the molecule. In order to determine the shape of the four-well potential, one has to utilize all data concerning the electronic structure available. In a first estimate, one could use the results obtained in the Hückel approximation [40-42] and from those calculate the electrostatic potential acting on the protons. By solving the Schrödinger equation for the two protons, one can then determine the probability distribution in their stationary states and from these data estimate the probability for the occurrence of "spontaneous errors" of the type discussed above. In this way, one can get a first rough idea of the whole phenomenon.

It should be observed that the problem of the two protons in the four-well electrostatic potential is actually a quantum-mechanical two-particle problem, and some of the methods previously developed for treating such systems could hence be utilized also in this connection. In a first approximation, the problem could be treated according to the independent-particle model, but, since the protons repel each other strongly, it seems desirable to introduce a certain amount of correlation between their motions. The previous experience gained in treating two-particle systems will here certainly turn out to be useful.

In conclusion, it should be observed that the separation of the electronic and protonic motions is an approximation. The protons will, of course, polarize the electronic clouds and, when the protons are moving, this polarization will shift and cause changes in the electronic structure. Since these changes will in turn influence the electrostatic potential acting on the protons, one obtains a "cycle" which may perhaps be treated by a self-consistent-field procedure. It is anticipated that these effects are comparatively small, but the problem is certainly of essential interest.

6. SOME REMARKS ON THE REPLICATION OF DNA, THE FORMATION OF RNA, AND THE CODING PROBLEM

It should be observed that, if the determination of the structure of the stationary form of DNA is a "static" problem, the question of the replication of DNA and the formation of RNA represents "dynamic" problems of a still higher degree of difficulty. In connection with the problems of "reading and transcribing the genetic code", it is hence much harder to reach conclusive results, and many of the arguments have to be rather speculative. In this section, we will not try to sketch any solutions to these problems but only give a review of some of the basic principles involved together with a brief summary of some of the mechanisms proposed by various authors. We will further emphasize some relevant points where experimental results could help in solving the problem. It should further be stressed that, even if the discussion of the biological functioning of DNA in Secs. 7-9 certainly depends on the mechanisms for "reading the code", the main results depend essentially only on the general copying principle - i.e. the complementarity concept for the nucleotides based on the proton-electronpair code for hydrogen bonding - and not on the detailed mechanism. After these words of precaution, we can now proceed to these details.

Replication of DNA. - In the original Watson-Crick model of DNA, it was simply suggested that, before the cell division, the two strands of the double helix would separate and that each one would then build its own complement leading to two new double-helices identical with the original one. Even if the basic principle is exceedingly simple, the actual mechanism involved may be rather complicated. The following three physical laws valid in both classical

physics and quantum theory have undoubtedly to be satisfied:

1) Conservation of Energy. - The main argument against the strand separation hypothesis in the Watson-Crick model comes from the fact that it would require a very large amount of energy to break all the hydrogen bonds in the DNA double helix simultaneously. It seems instead more feasible to assume a mechanism where the synthesis of the complementary strands goes parallel with the strand separation in the original helix, so that at least part of the energy gained in the formation of the 4-6 new hydrogen bonds could be used to break the 2-3 hydrogen bonds in another base pair in the old double helix. Since the net result is that one has formed two double helices from one double helix and free nucleotides, the energy totally released depends on the number of hydrogen bonds formed in one helix with a correction for the energy amount involved in linking the sugar-phosphate backbones together.

2) Conservation of Momentum. - This physical law implies that the masscentrum of the total system (old double helix plus nucleotide building material, enzymes etc.) will not be changed under the replication process, unless there is some interaction with the boundaries. Assuming that there is no environment which easily can pick up a large amount of momentum, one finds that the two "daughter helices" resulting are at least approximately at rest with respect to each other or moving in opposite directions with about the same velocity.

3) Conservation of Angular Momentum. - It is clear that, in a process where the synthesis of the two new strands goes parallel with the breaking up of the old helix, there will undoubtedly be a complicated winding-unwinding problem. In this connection, it should be observed that the total angular momentum of the total system (old double helix plus nucleotide building material, enzymes, etc.) has to remain constant under the entire replication process. If one imagines that part of the system rotates in a certain direction around an axis, there should hence also be another part of the system rotating in opposite direction around the same axis. Assuming that there is no environment which can easily pick up angular momentum, one finds that the two "daughter helices" resulting should have no rotation at all or rotate with opposite directions around the same axis.

In discussing various types of replication mechanisms, it is further often clarifying to use a terminology introduced by Delbrück and Stent [50] and

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50) M. Delbrück and G.S. Stent, "The Chemical Basis of Heredity", 699 (Johns Hopkins Press, Baltimore 1957).

which distinguishes between conservative, semi-conservative, and dispersive replication. In considering a given parental substance and its daughter duplexes after one or several replications, one says that a process is conservative if, among all the duplexes, there is one which is entirely parental and the rest are completely new. A process is semi-conservative; if the parental substance consists of two equivalent parts which are at the first replication divided between the two daughter duplexes so that, after an arbitrary number of replications, there are exactly two duplexes which contain the two parts of the parental substance; which are then said to be the conservative elements of the process. A process is finally dispersive, if the parental substance after several replications has become distributed in small pieces among several of the duplexes. We note that, in this general classification, it is not necessary to make any specific assumption about the character of the parental substance itself. The original Watson-Crick model implies apparently a semi-conservative replication mechanism, where the DNA double-helix is the parental substance and the strands are the conservative elements which are kept intact in a series of replications.

One of the first attempts to deal with the winding-unwinding problem was made by Delbrück [51], who assumes that the complementary synthesis proceeds

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51) M. Delbrück, Proc. Nat. Acad. Sci. U.S. 40, 783 (1955).

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synchronously along the two strands and that, as the synthesis proceeds, the strands break at the growth point at every half-turn of the helix (every fifth link) to have the lower terminals of the breaks immediately rejoined to the open ends of equal polarity of the new strands. This leads to a dispersive replication mechanism.

Another possibility was suggested by Bloch [52]. In his model, there is at the start no unwinding of the sugar-phosphate backbones; after breaking the hydrogen bonds in each base pair, each base is instead turned 180° around the glycoside bonds to open up the "proton-electronpair code" to form a template suitable for synthesis. After formation of two complementary strands on this template, one obtains a four-stranded intermediate compound. The new hydrogen bonds are then broken, the new strands are separated from the old strands, and two standard double helices are formed by rotating all bases 180° around the glycoside bonds to the proper positions for hydrogen-bond formation within each

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52) D.P. Bloch, Proc. Nat. Acad. Sci. U.S. 41, 1058 (1955).

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complex. The parental helix is then restored and, in addition, one has obtained an identical daughter helix. The use of nucleotides with the base planes rotated 180° around the glycoside linkage has been severely critizised by Crick [53] for steric reasons, but the model is anyway interesting as an example of a conservative replication mechanism.

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53) F.H.C. Crick, "The Chemical Basis of Heredity", 532 (Johns Hopkins Press, Baltimore 1957).

The so-called Y-model (see Fig. 6) has been studied in greater detail by Levinthal and Crane [54]. They point out that, "by an appropriate combination

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54) C. Levinthal and H.R. Crane, Proc. Nat. Acad. Sci. U.S. 42, 436 (1956).

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of rotations of the vertical part and the arms (each on its own axis), all the requirements of the unwinding of the parent and the coiling of the progeny can be satisfied without the Y changing its orientation in space. All that will happen to the Y will be gradual shortening of the vertical part and lengthening of the arms together with a spinning of all three branches". Their calculations show that the procedure "involves requirements of mechanical strength and energy production which are well within those available and that it is the favored type of motion from the standpoint of the viscous drag". However, since all the three branches of the Y rotate in the same direction, and the speed cannot be too low, there seems to be a rather large amount of total angular momentum required in this model, and the source is not known. The mechanism represents probably the simplest realization of the Watson-Crick model and is a typical example of a semi-conservative replication procedure.

We have now given one specific example of each type, but many more have actually been suggested by various authors. A conservative scheme proposed by Stent [55] will be treated in connection with the RNA-formation. For a more complete survey, we will otherwise refer to the review articles by Delbrück and Stent [50] and by Williams [56].

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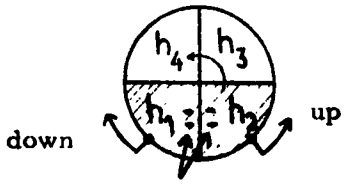
55) G.S. Stent, Adv. Virus Research 5, 95 (1958).

56) R.C. Williams, Revs. Modern Phys. 31, 233 (1959).

An important step towards the solution of the problem of the replication mechanism was taken through the experiments by Meselson and Stahl [57] who by means of a radioactive trace element (N^{15}) could show that the procedure in E. coli is characterized by the fact that "the nitrogen of a DNA-molecule is divided equally between two physically continuous subunits; that, following duplication, each daughter molecule receives one of these; and that the subunits are conserved through many duplications". The process is hence definitely semi-conservative. So far, it has not been conclusively shown that the intact subunits are identical with the single strands in the DNA-molecule, but the experiment gives otherwise strong support to the Watson-Crick model.

57) M. Meselson and F.W. Stahl, Proc. Nat. Acad. Sci. U.S. 44, 671 (1958).

The Quadruple Helix. - Let us for a moment return to the Watson-Crick model and the winding-unwinding mechanism. It is clear that the two strands of the double helix have to be separated to form a template, but, instead of moving the strands outside the original helix and its protein wrapping as in the Y-model, we will now investigate what possibilities exist inside the helix itself. It should be observed that, with respect to the axis of the helix, each base covers an angle of about 90°, so that there is actually space for totally four helices without any closer packing of the sugar--phosphate backbones than in the original double helix. We will denote the possible helix positions by h_1, h_2, h_3, and h_4.



proton code

Considering the normal double-helix with the base pairs filling the positions h_1 and h_2, we will start by giving a simplified picture. If one could break all hydrogen bonds simultaneously, one could rotate the entire helix h_2 freely around the axis without any distortion into the position h_4 with the formation of one new hydrogen bond, and the structure would then have the proton--electronpair code in an open position [58]. More symmetrically, one could rotate

58) The possibility of this rotation to "open the code" has actually been suggested by Crick, reference 53, as an alternative to Bloch's rotations of the bases around the glycoside bonds.

the helices h_1 and h_2 an angle of 90° each in opposite directions to the positions h_4 and h_3, respectively; see Fig. 8. In this "replication form", the two sugar-phosphate backbones are moved more behind the base pairs than before, so that it would be easier to move nucleotides into the helix itself; at the same time, the proton code is still rather well shielded against outer disturbances which could change the genetic message. In this form, the entire double helix serves as a template and, since each plane contains one purine and one pyrimidine base, the steric conditions are strongly emphasized. Each base will now only accept a partner which will fit both the hydrogen-bond code and the helix's geometry; see Figs. 9 and 10. In this connection, one should observe how important it is that the sugar-phosphate backbone has the deoxy-ribose form, since there would otherwise be OH-groups attached both at the $C_{2'}$- and $C_{3'}$-positions which may lead to ambiguities.

After conclusion of the synthesis according to the complementarity principle, one would have a quadruple helix with the two pairs $h_1 - h_2$ and $h_3 - h_4$ joined by the conventional hydrogen bonds (4 - 6 bonds in total), whereas the two halves would be joined by two presumably "hot" hydrogen bonds. So far, the synthesis has not involved any "spinning" at all, but the two double helices $h_1 - h_2$ and $h_3 - h_4$ could now be separated by rotating in opposite directions with respect to each other in a state where the total momentum and the total angular momentum would by compensation still be vanishing; the energy required could come from the extra hydrogen bonds formed in the process. Since the process is semi-conservative, it would be completely in agreement with Watson-Crick's model.

In the procedure sketched above, there are no steric deformations of the sugar-phosphate backbones or bases involved, and the nucleotides may actually be considered as rigid building stones. It is evident, however, that, depending on the large initial energy required, the process must follow a more complicated pattern where one can utilize the previously mentioned process involving simultaneous synthesis and decomposition, i.e. where part of the energy released in the formation of every two new base pairs (4 - 6 bonds) could be utilized to break 2 - 3 hydrogen bonds in the old helix. This implies that, at a given time, only a very small part of the original helix will be in "replication form", whereas the main part of the helix will still be in the normal form; see Fig. 10. In the short region between the two forms, the helix is in an intermediate structure with the sugar-phosphate backbones slightly deformed but these steric disturbances are not severe and are completely removed after

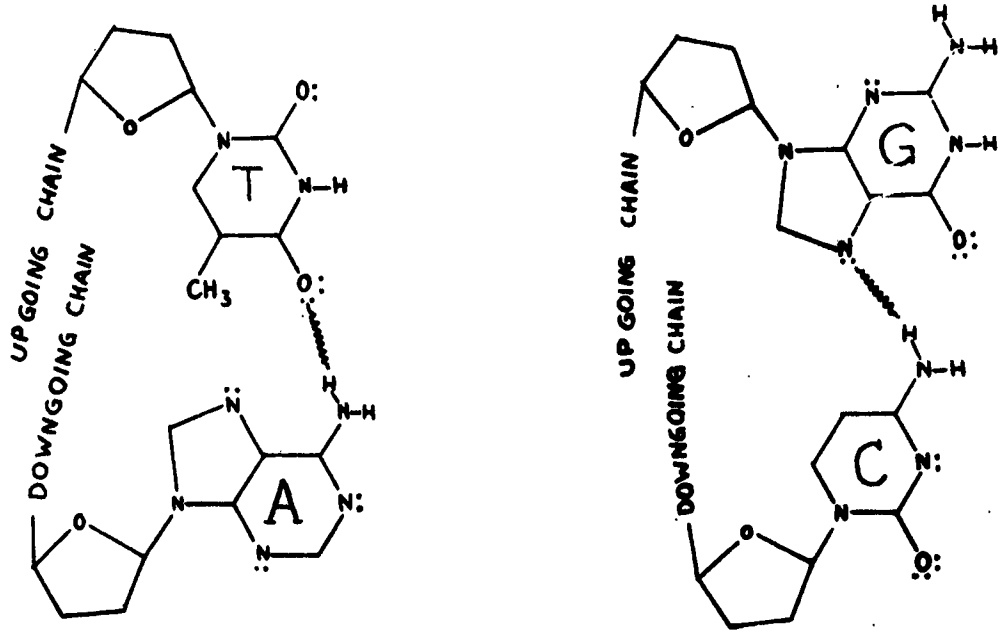


Figure 8. The nucleotide base pairs in a suggested "replication form" with the proton-electronpair codes open for the addition of a pair of complementary bases. The symbol ---------- indicates a presumably "hot" hydrogen bond; see text.

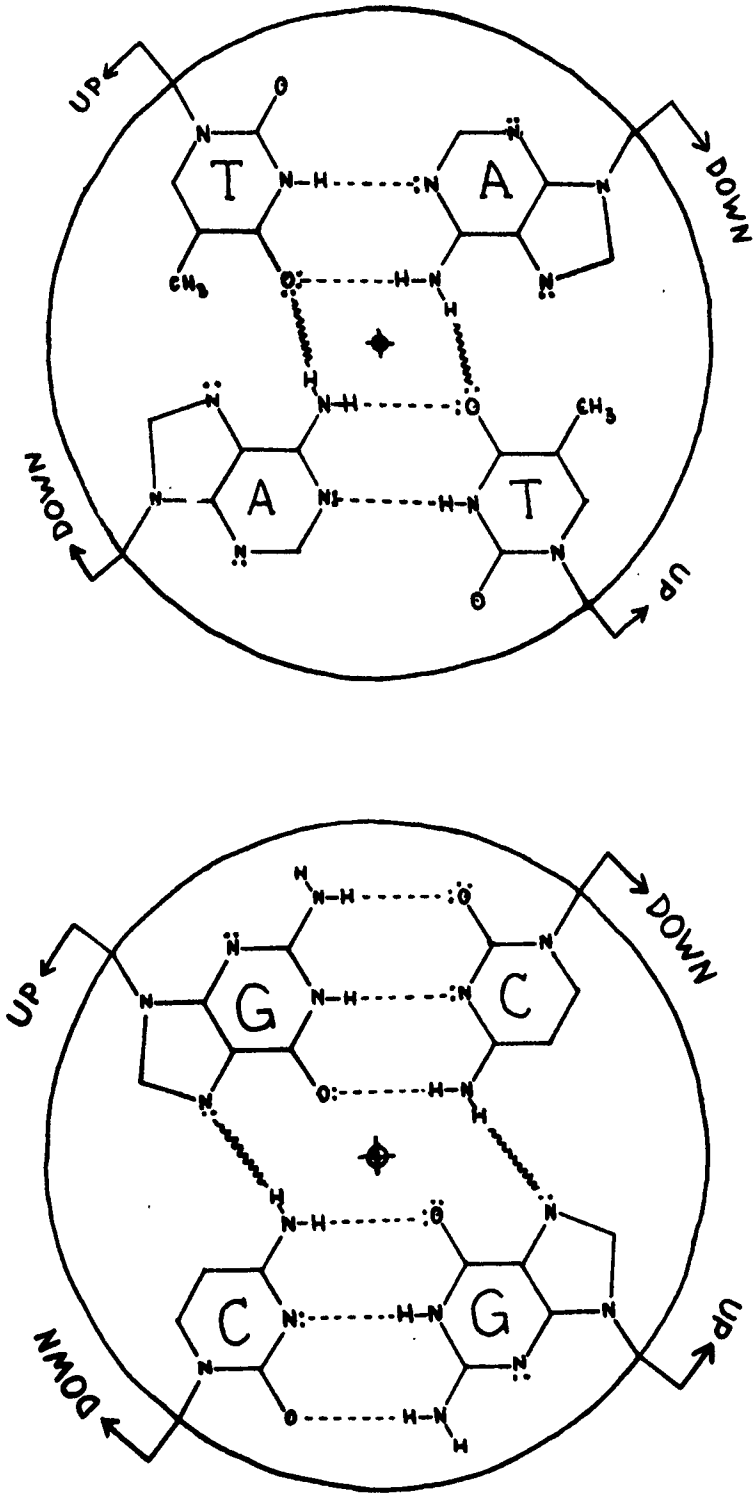
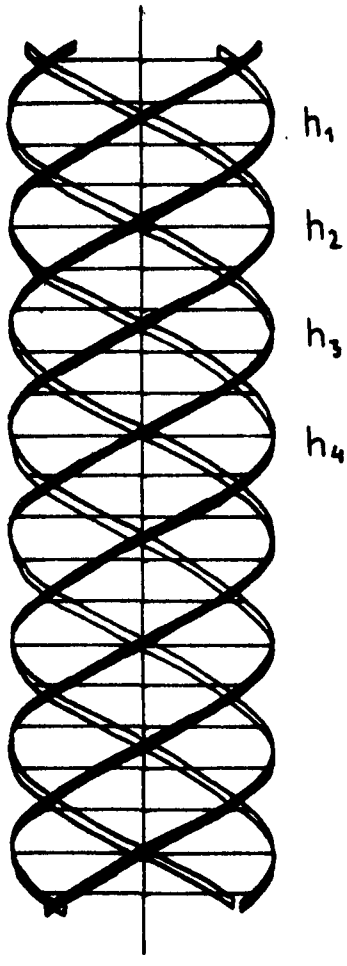


Figure 9. The base planes of the suggested quadruple-helix; the two pairs are afterwards broken by releasing the hydrogen bonds indicated by the symbol ~~~~~ and denoted as "hot".



Quadruple helix
with base planes
indicated

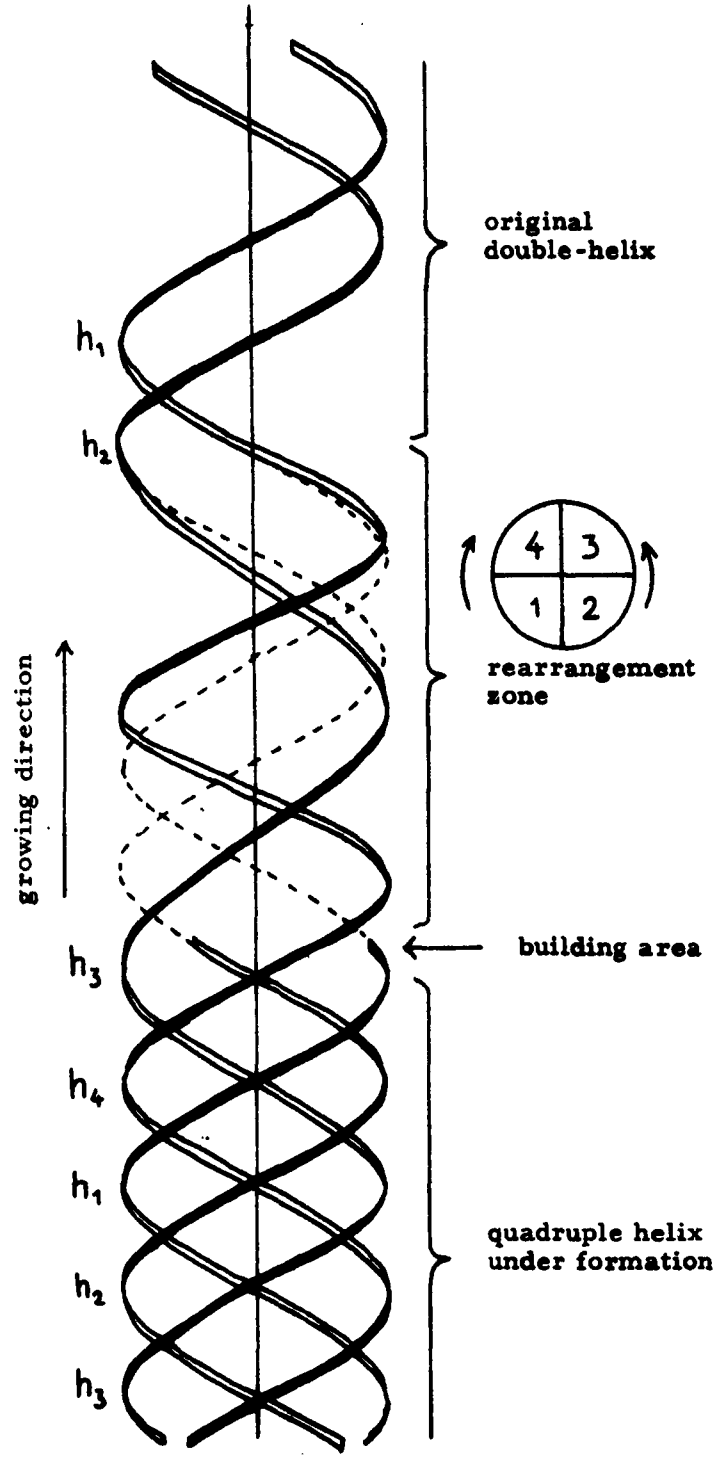


Figure 10. Formation of quadruple helix in suggested mechanism of DNA-replication.

the formation of the quadruple helix. This means also that the double helix never appears in its full length as a template; instead the synthesis proceeds continuously along the helix with the formation of two base pairs at the time in a way which also facilitates the necessary enzyme action and keeps the genetic code shielded.

The model indicates that, during a certain stage of the interphase, there ought to be a DNA-molecule with twice as high molecular weight as the normal form. In addition to the study of the quadruple helix, one ought to investigate also the possibilities for the formation of a "double-length" double helix after the uncoiling process is concluded.

Such double-weight DNA-molecules have actually been experimentally observed by Cavalieri and Rosenberg [59], but they interpret their results in a completely different way. According to their opinion, the replication process is semi-conservative in agreement with the experiment by Meselson and Stahl [57], but the parental substance consists of two DNA double-helices joined by special (biunial) bonds and the conserved unit is a full double-helix [59a]. Since their scheme deviates considerably from the Watson-Crick model, it would certainly be of essential interest to study the detailed structure of the heavy DNA-molecule by means of X-ray diffraction to see whether it could have any relation to the quadruple helix and double-length helix discussed here.

In conclusion, it should be observed that the replication form of the DNA molecule may be of importance also in the mechanisms of genetic recombination, since it may provide a simple mechanism for exchange of parts of strands between two double helices.

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59) L.F. Cavalieri and B.H. Rosenberg, Biophys. J. 1, 317, 323, 337 (1961).

59a) For a replication scheme compatible with this picture, see e.g. A.L. Dounce, J. Theor. Biol. 2, 152 (1962).

Formation of RNA. - The hereditary substance should not only have the property of being self-replicating but also have the ability of transcribing the genetic message to the cell and the organism. As pointed out in Sec. 3, there seem to be good reasons for believing that the genetic code is transferred from the DNA-molecule to the ribosomes in the cytoplasm, where the actual protein synthesis takes place, by means of a special polynucleotide called messenger-RNA.

If the mechanism of the DNA-replication is rather uncertain, the actual procedure involved in the formation of this messenger-RNA is still less known. Experimental evidence [60] indicates, however, that the base ratios of this RNA are closely analogous to those found in the DNA regulating the formation, and it seems hence natural to assume that DNA in some way acts as a template. In this section, we will briefly review some of the attempts which have been made to describe the transcription mechanism itself.

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60) E. Volkin and L. Astrachan, Virology 2, 149 (1956); A.N. Belozersky and A.S. Spirin, Nature 182, 111 (1958); E. Volkin, L. Astrachan and J.L. Countryman, Virology 6, 545 (1958); M. Ycas and W.S. Vincent, Proc. Nat. Acad.Sci. U.S. 46, 804 (1960); E. Volkin, Proc. Nat. Acad. Sci. U.S. 46, 1336 (1960); M. Nomura, B.D. Hall, and S. Spiegelman, J. Mol. Biol. 2, 306 (1960); A. Stevens, J. Biol. Chem. 236, PC43 (1961).

The double helix of DNA has a shallow groove and a deep groove which are both rich in protons and lone electron pairs. Today, it is believed that the shallow groove is occupied by a helical protein (histone) which helps in stabilizing the entire molecule [61], whereas the role of the deep groove is not yet fully known. It was observed by Stent [62] that the deep groove contains a proton-electronpair code which may serve as a template for a third helix which

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61) See e.g. M.H. Wilkins, "The Structure of the Nucleic Acids and Their Role in Protein Synthesis" (Cambridge University Press, 1957).

62) G. Stent, Adv. Virus Research 5, 95 (1958).

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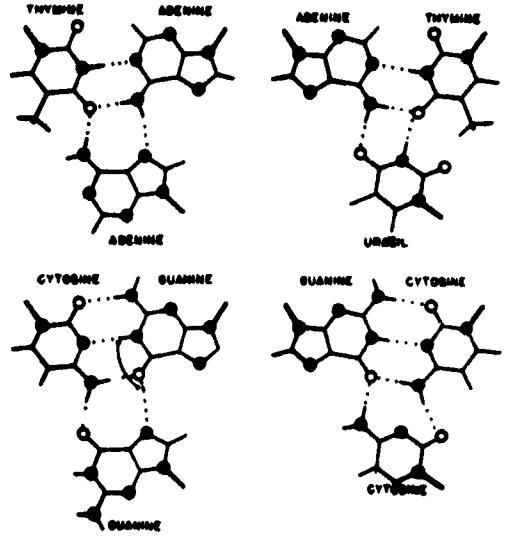
would fit into this place. The hydrogen bond formation suggested by Stent is given below:



In these figures, filled and open circles represent nitrogen and oxygen atoms, respectively; the little arrow indicates a tautomeric shift. If one actually builds a stereo-model of this triple helix, one finds that, in order to obtain a connecting sugar-phosphate backbone for the third helix, it is necessary in two of the cases to rotate the entire side-chain in the nucleotide 180° around the glycoside bond. However, according to Crick [53], this form of the nucleotides seems sterically to be rather unprobable.

Of crucial importance in the problem of the DNA-RNA transcription is the question of the relation between the two quotients:

$$\left(\frac{G+C}{A+U}\right)_{RNA} \quad , \quad \left(\frac{G+C}{A+T}\right)_{DNA} \quad .$$

Two more triple helices have been suggested by Zubay [63], and they have the transcription characteristics:

Model A	Model B
TA → C	TA → A
AT → G	AT → U
CG → U	CG → G
GC → A	GC → C

63) G. Zubay, Nature 182, 1290 (1958); Proc. Nat. Acad. Sci. U.S. 48, 456 (1962).

They are described in greater detail in Fig. 11. Both are within certain margins sterically reasonable. Since some of Zubay's experiments [64] indicated that the values of the abovementioned base ratios were the inverse of each other, Zubay favored "model A" and wanted "model B" eliminated. On the basis of other experiments [60], one may today feel more inclined to favor "model B", and a more complete discussion of this problem will be given below.

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64) G. Zubay, Nature 182, 112 (1958).

Experiments with synthetic polynucleotides [65] have shown the existence of three-stranded helical molecules, and particularly polyinosic acid with three hypoxanthine bases in the plane is remarkable because of the symmetry in the hydrogen bonding between the constituents. Study of such three-stranded complexes is certainly of value in this connection.

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65) A. Rich, Nature 181, 521 (1958); Biochim. et Biophys. Acta 29, 502, (1958); Revs. Modern Phys. 31, 191 (1959); Proc. Nat. Acad. Sci. U.S. 46, 1044 (1960).

An important experiment concerning the nature of the DNA-RNA transcription in the bacteriophage T2 has recently been reported by Hall and Spiegelman [66]. They have found that the RNA molecules synthesized in the bacteriophage-infected cells of E. coli have the ability to form a well-defined complex with denaturated DNA of the virus. From the formation of this hybrid, they conclude that there must exist a perfect, or near-perfect, complementarity between the nucleotide sequences of T2-DNA and RNA in the sense of Watson and Crick. "The demonstration of sequence complementarity between homologous DNA and RNA is happily consistent with an attractively simple mechanism of informational RNA synthesis in which a single strand of DNA acts as a template for the polymerization of a complementary RNA strand". Let us now study the conditions for such a mechanism in greater detail.

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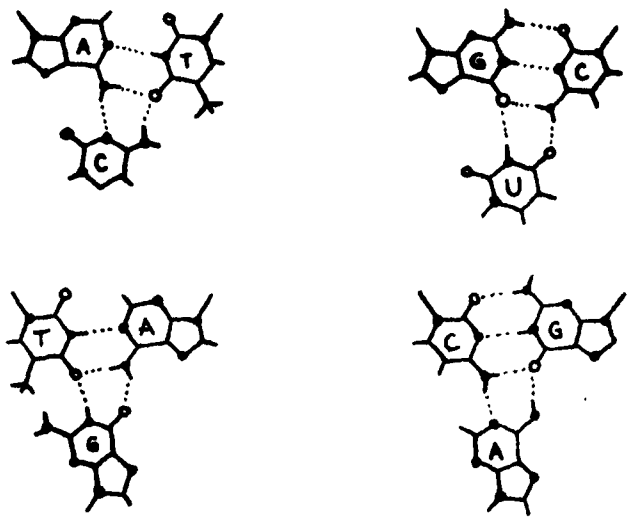
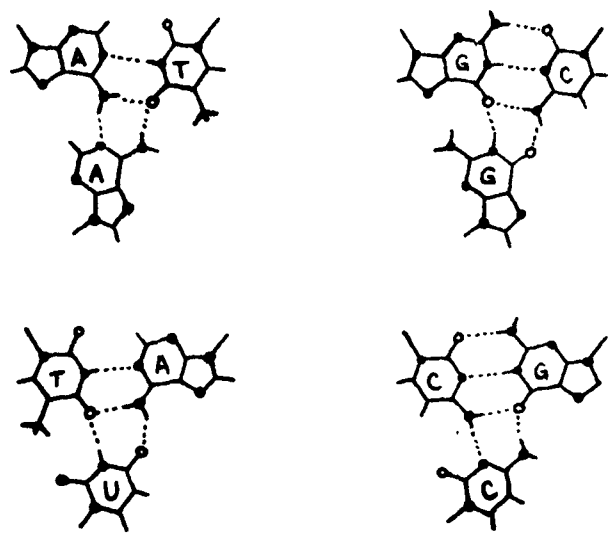
66) B.D. Hall and S. Spiegelman, Proc. Nat. Acad. Sci. U.S. 47, 137 (1961).

In investigating the normal base pairs (see Fig. 5), one finds immediately that the proton-electronpair core exposed by the left-hand base also occurs in



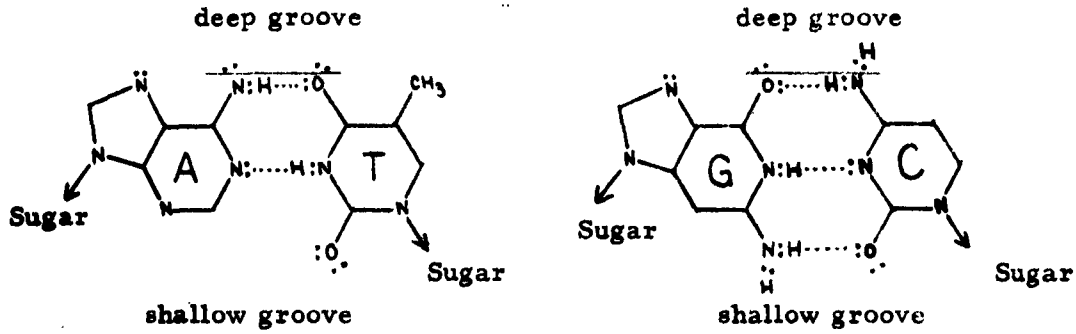
Model A



Model B

Figure 11. Combination of a DNA base pair and a third nucleotide base in the deep groove of DNA according to Zubay [63]. Filled and open circles represent nitrogen and oxygen atoms, respectively. Note that the lowest base in each figure represents the RNA component.

the "deep groove":



The distance between the proton and the lone-pair concerned is, however, considerably longer than in the base, and also the angular structure needs improvement. The situation becomes much more ideal for "transcription", if one can rotate the base pairs around the axis somewhat towards each other, say 15 - 30°, to get a better analogy with the structure of polyinosic acid mentioned above [65]. It should be observed that this rotation of the two helices should be possible without breaking the bonds with the histone wrapping in the shallow groove, since the protein chain contains some extra folds. This operation brings the double helix into a "replication form", and a third helix can now easily be added in the deep groove with the base determined by the hydrogen bonding as indicated in Fig. 12.

A few words should perhaps be added about the geometry of the third helix. Since the pyrimidine bases are considerably "shorter" than the purine bases, it turns out that, in the attached pentose groups, the 3'-position of the former is approximately equivalent with the 2'-position of the latter. This implies also that it seems possible to build a sugar-phosphate backbone only if both the 2'- and the 3'-positions are available, i.e. carry a hydroxyl group, and this would then explain why the third helix would be required to have ribose--character and be RNA. If this picture is correct, messenger-RNA should show C'_2 - C'_5 linkage as well as C'_3 - C'_5 linkage [67].

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67) Compare the discussion in J.N. Davidson, "Nucleic Acids" (Methuen and Co., London 1960), particularly p. 41-44.

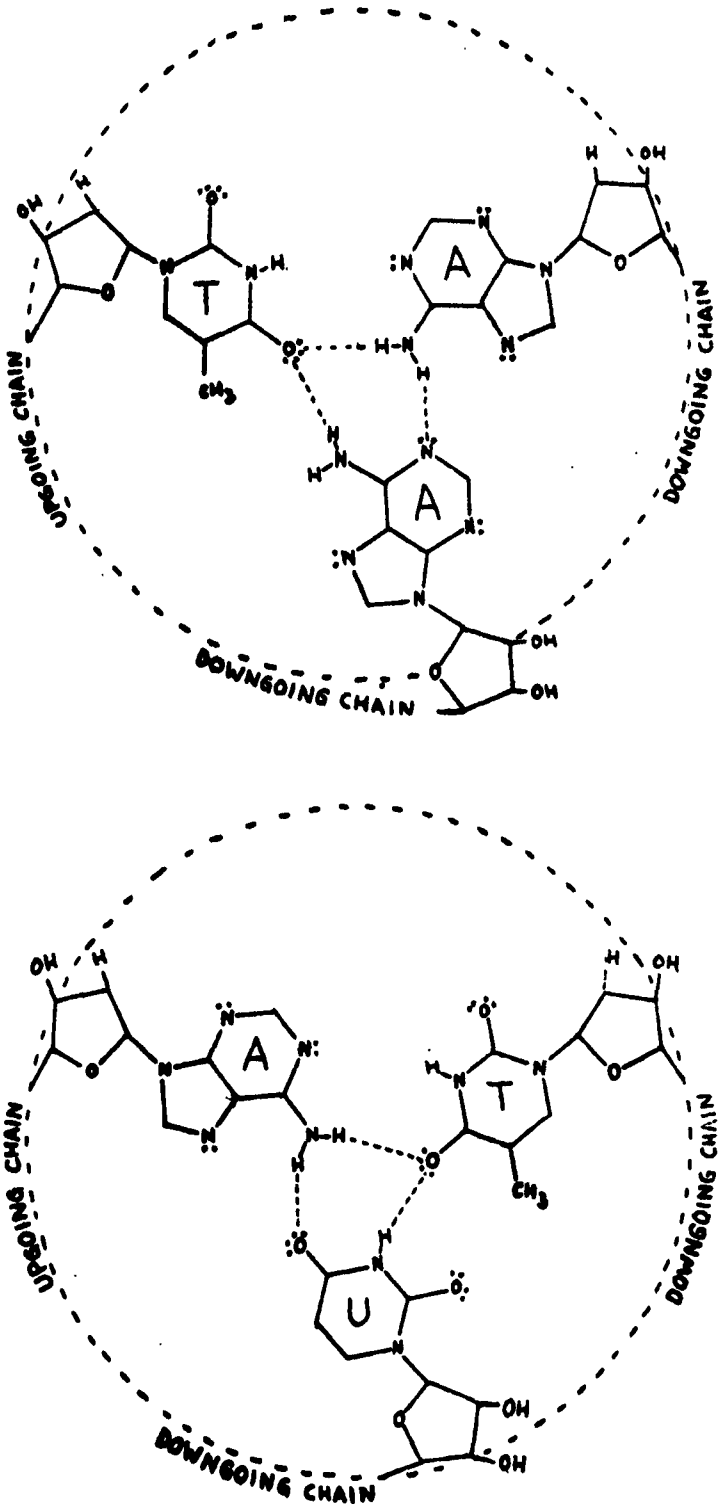

Figure 12a. Combination of DNA base pairs and a third nucleotide base in the deep groove of DNA in "replication form".

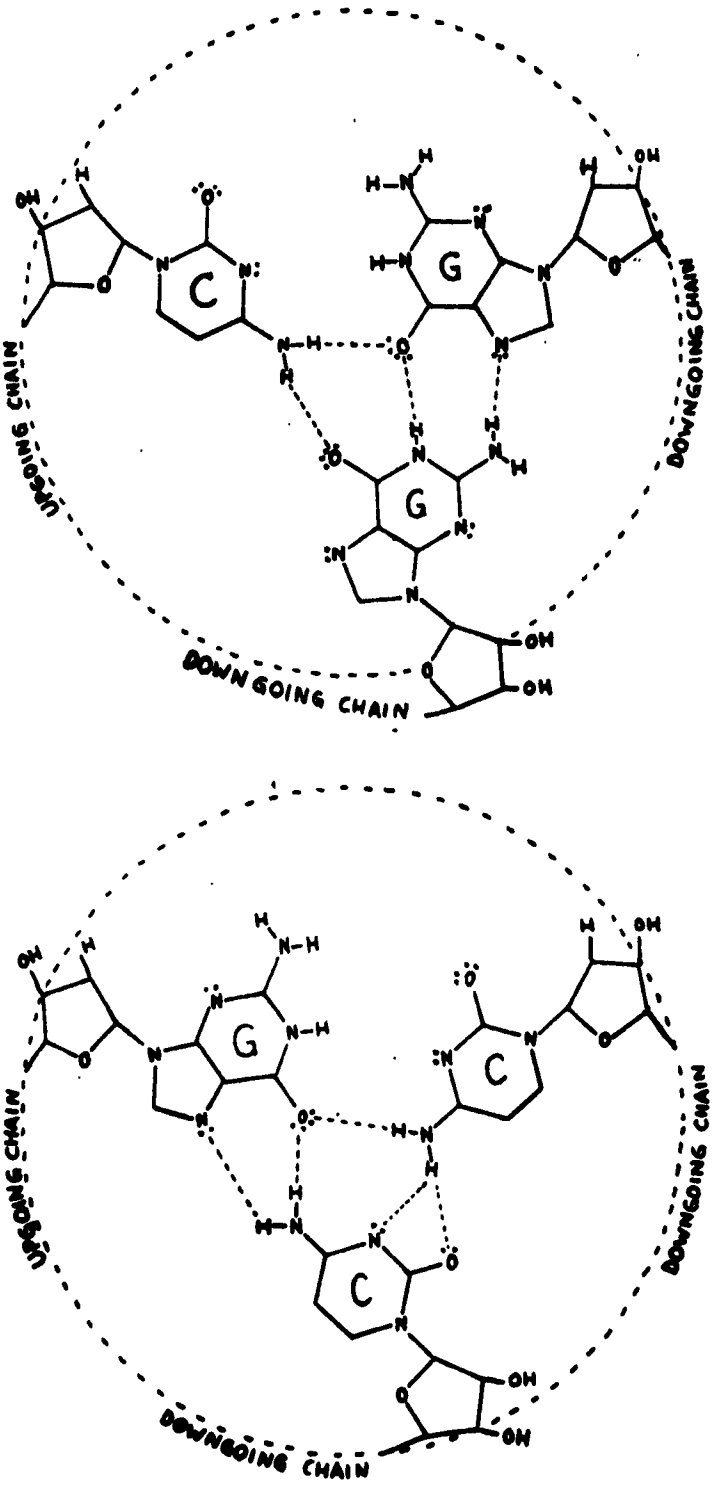

Figure 12b. Combination of DNA base pairs and a third nucleotide base in the deep groove of DNA in "replication form".

Such a picture implies further that, under certain conditions, a pyrimidine base may be replaced by a code-equivalent purine base, so that uracil may be replaced by guanine and cytosine by adenine. However, the replacement shows up in the linkage of the sugar-phosphate backbone and should perhaps not be considered as a real degeneracy. It should also be observed that the experiment by Hall and Spiegelman [66] does not necessarily prove complete complementarity in the sense of Watson and Crick; it is probably sufficient for the formation of the hybrid that the strands involved are complementary with respect to the hydrogen-bonding alone.

It is evident from Fig. 12 that only one of the strands of the double-helix DNA will be "read" in the transcription procedure, as the formation of RNA proceeds along the axis. As in the replication of DNA, the energy released in forming new hydrogen bonds will be used to break previously formed bonds, which means that, at the end of the procedure, the newly formed RNA strand will be practically free from the double helix. However, there remains the difficulty that the new RNA molecule is coiled an immense number of times around the axis of the DNA molecule and has to be separated to serve as a "messenger". It should further be observed that, since only one strand of DNA has been read, one could understand the similarity between the ratios (G + C) : (A + T) for DNA and (G + C) : (A + U) for RNA in case of no degeneracy, but hardly any other relation concerning the base ratios.

These difficulties are all solved simultaneously, if one assumes that the transcription process does not stop at the end of the DNA-molecule but goes back to the starting point. One could think of the enzyme-system as a "ring" moving up and down the DNA fiber at least the distance of a "gene". The first part of the RNA strand is successively moved out of the deep groove, and the procedure is continued as before, which means that, in going back, the other strand of DNA is being read. When the process has reached the starting point again, there has been synthesized a single-strand molecule with a "loop" connecting the two RNA halves coming from the two DNA-strands. Since the return procedure implies also an unwinding from the helix axis, the RNA is at the end free from the DNA molecule. If there would be no degeneracy, the base composition of the two halves of RNA would be an exact copy of the base composition of DNA and, according to Chargaff's first law, one would have A = U and C = G. This RNA-molecule would further be characterized by the fact that it would be a single-strand molecule which would be identical with its own complement. However, if code-equivalent bases under certain conditions may

replace each other, so that A replaces C and G replaces U , one obtains instead A + C = G + U , i.e. the law Chargaff has found characteristic for RNA and expressed in the form "6-amino = 6-keto".

This type of reading procedure would finally also explain the remarkable tendency of the messenger-RNA molecule to fold back on itself without necessarily giving rise to a double helix (which partly may be prevented by the steric disturbances introduced through the abovementioned degeneracy). By using the arguments by Hall and Spiegelman, this tendency may be taken as an indication for the existence of at least code-complementarity between the two halves of the molecule.

It is hardly necessary to emphasize that a "transcription model" of this type should not be taken too seriously, since the experimental data available (and particularly Chargaff's second law) may certainly be interpreted in many other different ways. However, it stresses the important problem whether only one or both of the DNA strands are "read" in the formation of messenger-RNA and the associated protein synthesis. There seems to be some experimental evidence [68] as to bacteriophage DNA that both strands are read in "replication" since changes in one strand give rise to both wild type and mutant progeny, but little seems to be known about what happens in "transcription". Special biological functioning of the two DNA strands in transcription has recently been suggested by Paigen [69].

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68) D. Pratt and G.S. Stent, Proc. Nat. Acad. Sci. U.S. 45, 1507 (1959); I. Tessman, Virology 9, 375 (1959); W. Vielmetter and C.M. Wieder, Z. Naturforsch. 14b, 312 (1959).

69) K. Paigen, J. Theor. Biol. 3, 268 (1962).

On the basis of our discussion, it is finally easy to understand the relation between the coding mechanism outlined in Fig. 12 and those previously suggested by Zubay (Fig. 11). His "model B" is identical with the transcription we obtain in the reading of the "second" strand, whereas his "model A" represents the same transcription changed to code-equivalent bases, so that A $\longleftrightarrow$ C and G $\longleftrightarrow$ U.

Further experimental analysis of the base composition of messenger-RNA will reveal more information about the degeneracy problem and the importance of code-complementarity versus complete complementarity.

Coding Problem. - As pointed out in Sec. 3, it is believed that the protein synthesis in the ribosomes is regulated by an "adapter mechanism" as suggested by Crick and Hoagland [14]. Each one of the 20 amino acids is attached to an adapter in the form of a comparatively small molecule of soluble RNA (sRNA) which carries the amino acid to its correct place on the messenger-RNA by means of complementarity between a small nucleotide part of the adapter and the template. This process is subject of intense experimental study, and it has e.g. been found that the amino acid is always attached to the adapter in the same way [70], namely through a nucleotide terminal group of the

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70) See, for instance, F. Lipmann, W.C. Hülsmann, G. Hartmann, H.G. Boman, and G. Acs, J. Cell. and Comp. Physiol. 54, Sup. 1, 75 (1959).

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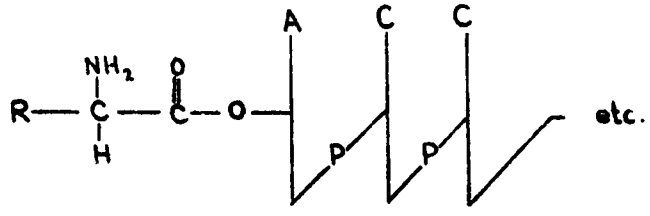

It is not yet completely clear whether the amino acid linkage goes to the 2' or 3' position of the pentose group in adenosine. The adapter contains, in addition to the nucleotide triplet or sequence characteristic for the adapter and its amino acid, quite a few other constituents which are now being investigated.

Let us now return to the coding problem treated in Sec. 3. According to Crick [24] et.al., the code ought to be a non-overlapping triplet code without commas which is read in triplets from a specific starting point. The overlapping codes were eliminated since they led to correlations between the dipeptides which do not exist in nature, and the "comma-less" codes had to be abandoned because of the existence of sense-triplets of the form UUU, as shown in the experiments by Nirenberg and Matthei [25]. The code is certainly degenerate, and the question is now how much can be said about the nature of the degeneracy. In this connection, one can follow part of the arguments given by Gamow provided that one changes the nature of the code to be non-overlapping instead of overlapping.

Let us start with the permutation-invariant code, in which the message is independent of the order of the three bases involved in the triplet. Since this code is equivalent with Gamow's "triangular code", it contains exactly 20 independent elements and each amino acid would have its unique triplet of letters. However, since the experiments [25] indicate that the coding letters for both leucine and valine may be U,U, and G, and for both glycine and tryptophane may be U, G, and G, this code should be excluded.

The direction-invariant code offers the next possibility. In this code, the message is independent of the direction the triplet is read, so that $B_1B_2B_3$ and $B_3B_2B_1$ are equivalent. The number of independent combinations is given below:

	BBB		$B_1B_2B_1$		$B_1B_2B_3$	
Number of combinations	4	+	12	+	24	= 40 ,

The total number is 40, and this may be reduced by a factor 2 by assuming that the middle position distinguishes only between 2 possibilities, so that the code is degenerate in this position with respect to complementarity (which leads to a non-overlapping code equivalent with Gamow's "diamond code"), or with respect to code-complementarity, code-similarity, and so on.

A somewhat different code is based on the assumption that, if both strands of the DNA double helix are read in their specific directions, they would contain the same message with respect to the protein synthesis. This means that the triplet $B_1B_2B_3$ should be equivalent with the triplet $B'_3B'_2B'_1$, where the symbol B' means the complementary basis to B . It leads to the diagram:

	BBB		$B_1B_2B_1$		$B_1B_2B_3$	
Number of combinations	2	+	6	+	24	= 32 ,

with 32 combinations. This strand-invariant code is easily reduced to only 20 independent elements by an additional assumption about a specific degeneracy. However, in the present situation, it is hardly worthwhile to go through all the mathematical possibilities, since a single experiment with synthetic polynucleotides could actually decide whether "strand-invariance" is another

possibility to be excluded or not. It is here mentioned mainly because the code is connected with the general problem of whether both strands of DNA are "read" in connection with the formation of messenger-RNA or not. A decision on this point would certainly be of importance.

In conclusion, we observe that we have here discussed the replication mechanism, the transcription procedure and the genetic code as if they all would be of universal nature. The existence of single-stranded DNA in the bacteriophage ϕX-174, the direct replication of the RNA of tobacco mosaic virus, etc., indicate that this can hardly be the case and that there must be many exceptions from the general pattern, or that this pattern itself is actually much more complicated than we now realize. In this connection, it may also be worthwhile to keep the general criticism expressed by Chargaff [71] in mind.

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71) E. Chargaff, "The Chemical Basis of Heredity" (Johns Hopkins Press, Baltimore 1957), p. 521.

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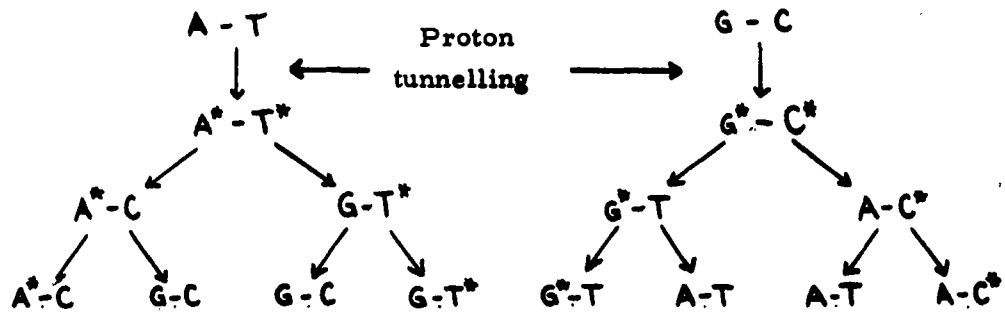
7. PROBLEM OF MUTATIONS

Spontaneous Mutations. - In this section of the paper, we will discuss some aspects of the biological functioning of DNA in view of the Watson-Crick model. Let us start with the problem of the spontaneous mutations and discuss them on the basis of the tautomeric mechanism. In the quantum-mechanical study of the properties of the hydrogen bond in Sec. 5, it was shown that there is a finite probability for simultaneous "proton tunnelling" through the potential barrier in the middle of the bond leading to the transitions

$$A - T \longrightarrow A^* - T^*, \qquad G - C \longrightarrow G^* - C^*,$$

showing that normal base pairs may be changed into pairs of tautomeric bases. If replication occurs in these forms, one can expect the following replication diagrams:



Hence the proton tunnelling leads to the following change of base pairs:

$$\begin{array}{lll} A - T & \longrightarrow & G - C \\ G - C & \longrightarrow & A - T \end{array}$$

where a base goes over into another base of the same type, i.e. a purine into a purine and a pyrimidine into a pyrimidine. Mutations of this type have been called "transitions" and are characterized by the fact that they are reversible.

In Sec. 5, we have also pointed out the existence of transformations of the normal base pair A - T to the forms $A^+ - T^-$ and $A^- - T^+$. For a neutral base pair, the probability for such a change is probably comparatively low, but the probability increases considerably if one of the bases in the pair is electrically charged. Since now the fundamental proton-electronpair code is lost, there will be difficulties in the replication scheme. There is actually no normal nucleotide which could combine with A^+ and T^+, and the occurrence of these ions may hence cause deletions in one strand of the base sequence, whereas the ions A^- and T^- lack code-specificity and may combine with all four normal bases. Since a deletion always means loss of genetic information, the corresponding mutation would be irreversible.

According to some authors [72], irreversible mutations would depend essentially on "transversions" i.e. changes of base pairs where a purine base is replaced by a pyrimidine base, and vice versa. The essential importance of deletions (and additions) in this connection have recently been emphasised by Crick [73] et.al.

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72) E. Freese, J. Mol. Biol. 1, 87 (1959); Proc. Nat. Acad. Sci. U.S. 45, 622 (1959). See also R. Sager and F.J. Ryan, "Cell Heredity" (John Wiley and Sons, New York 1962).

73) S. Brenner, L. Barnett, F.H.C. Crick, and A. Orgel, J. Mol. Biol. 3, 121 (1961).

It should be observed that, in addition to the replication errors occurring because of tautomeric changes in the original DNA-molecule, there may also be "incorporation errors" depending on the fact that the new nucleotide material may contain bases in the rare tautomeric forms A^*, G^*, T^*, and C^*. It would be interesting to know the molar fractions of these forms occurring in a "tautomeric equilibrium" but, at the same time, one has to remember that the biochemical situation in the cell nucleus is probably far away from this equilibrium. If the Watson-Crick model for replication should work, one can instead expect that the new nucleotides entering DNA-replication should be in their "normal" forms as much as possible. The mechanism involved is not known but is certainly worthwhile studying. However, whatever the "purification" procedure can be, it can hardly avoid the quantum-mechanical tunnel-effect, and a small portion of the new material should hence also appear in tautomeric form. The total number of mutations will thus depend both on internal errors in the genetic code and on incorporation errors.

Since the proton transfer occurring in all these tautomeric changes is a typical quantum-mechanical phenomenon depending on the "tunnel effect", one can say that the transition to the rare forms involves a quantum jump of the DNA-molecule between two stationary states. The model is hence in complete agreement with the general idea about mutations expressed by Delbrück and by Schrödinger and discussed in Sec. 2. However, there is a difference with respect to the details of the picture, since Delbrück thought that it would be necessary to bring the system above the energy treshold leading from one state to another (as in ordinary chemical reactions), whereas actually the proton transfer goes through this potential barrier by means of the tunnel effect.

Induced mutations. - In addition to the spontaneous mutations, there are mutations induced by certain chemicals (mutagens) and by radiation [74]. The

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74) See e.g. "Mutation", Brookhaven Symp. Biol. 8, 1956 (U.S. Dept of Commerce, Washington 1956).

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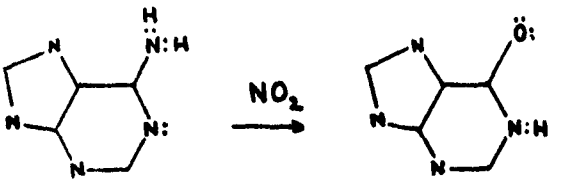
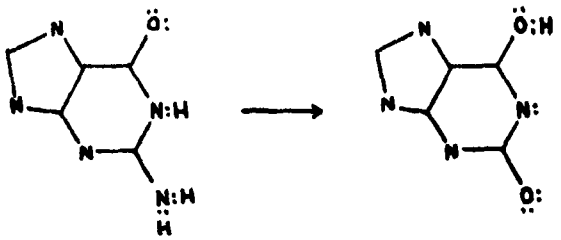
simplest mutagens are those which cause a major change in the bases themselves connected with a change in the proton-electronpair code, e.g. nitrous acid which

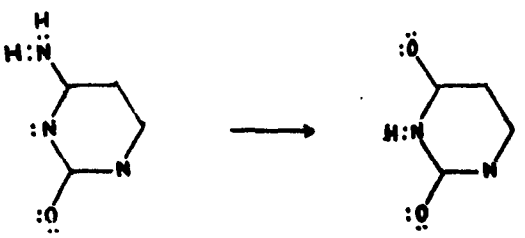
causes an oxidative deamination of the bases:



adenine hypoxanthine (guanine code)

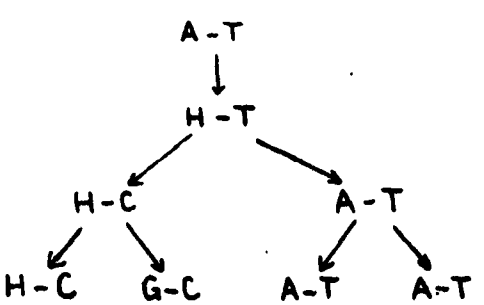


guanine xanthine (adenine code)



cytosine uracil (thymine code)

Since the base code has been changed, the process will necessarily induce mutations as, for instance, in the diagram below:



H = hypoxanthine

Other types of mutagens may just shift the π-electron cloud around the positions 1 and 6 enough to induce a proton transfer within a base and lead to a tautomeric form. Mutations may also be caused by adding base-analogs (like 5-bromouracil) in the synthesis of DNA. If the base-analog has two tautomeric forms, where the positions 1 and 6 are more equivalent than in the original bases, the base analog may be accepted in one form but, after proton transfer, it may replicate in the other form leading to a genetic error. This process may be of essential importance in destroying the genetic code in cells or organisms which are for some purpose not desired.

It has previously been pointed out that mutations of the second type, where A - T goes over into $A^+ - T^-$ and $A^- - T^+$ may be caused by inducing unequal charges in the two bases. This can be done by adding or subtracting electrons or protons. Certain chemical compounds (often in the form of conjugated systems) may be supposed to enter into donor-acceptor reactions with the normal base pair, but it is observed that only very special types have a mutagenic effect. This may be caused by the fact that the base pairs are normally extremely well shielded so that, in order for the mutagen to interact with them, it is necessary that it can reach them, for instance by being attached to the special proteins which catalyze the DNA-replication itself. Attention should also be devoted to the possibility for protons (or small positive groups) moving in the environments of the base pairs to get attached to some of the extra lone pairs existing, since this will give an extra charge to the base involved. Another important point is the removal of an electron through ionizing radiation, which may have a more or less direct influence. The effect of electron or proton "bombardement" has so far not been sufficiently studied.

In conclusion, it should be mentioned that one may expect induced mutations if the electrostatic double-well potentials in the hydrogen bonds are disturbed by an outer electric field. It seems hence worthwhile to carry out experiments involving the growing of cultures in specially applied electric fields or on plasts or other materials which have a large ability to keep high electrostatic charges for a very long time in the form of double layers.

Theory of Evolution. - It is evident that the mutations must play a most important role in the theory of evolution. The first polynucleotide with the property of self-replication has been called the first "living thing" on earth [75]. This

75) N.H. Horowitz, Proc. Nat. Acad. Sci. U.S. 31, 153 (1945); see also A.I. Oparin, "The Origin of Life" (Dover Publications, New York 1953); "International Symposium on the Origin of Life on the Earth" (Ed. A.I. Oparin, Pergamon Press, London 1959).

molecule may actually have been rather small, and it is remarkable that the mechanisms of replication and mutation seem sufficient to explain the synthesis of the enormously long DNA-molecules which are characteristic for the higher organisms.

If the small polynucleotide has the power of self-replication, it has probably also (under certain conditions) the ability of doubling its own length by adding the copy to the original. The replication of DNA by means of the quadruple helix seems particularly convenient for such a procedure, if there would be a mechanism so that the two double helices could be joined to each other in the final stage of their separation. The process could be repeated and would lead to a long DNA-molecule containing the same genetic message associated with the original polynucleotide repeated over and over again. However, due to influence of proton tunnelling and mutations, the base sequence may be altered with time and get a more complicated character. In the struggle for the nutrition material, the principle of "natural selection" would then start working.

It would take us too far to go any deeper into the theory of evolution here, and we will only give a few references. It is evident, however, that the question of the base composition of DNA and the order of the base sequence represent very important problems in this connection. In a study of the process of evolution, the Pullmans [76] have carried out a quantum-mechanical investigation of the four bases and have found that cytosine has very likely the highest probability to go over into its tautomeric form, but they have, so far, not considered the effect of proton tunnelling in base pairs. The question of sequence distribution and neighbour effects has been treated by Simha and Zimmerman [77], and the problem as to the evolution of base composition has been studied by Freese [78].

76) B. Pullman and A. Pullman, Technical Note No. 86, Uppsala Quantum Chemistry Group (1962).

77) R. Simha and J.M. Zimmerman, J. Theor. Biol. 2, 87 (1962).

78) E. Freese, J. Theor. Biol. 3, 82 (1962).

8. PROBLEM OF AGEING

The problem of the cause of ageing has always been of great interest, and one has particularly pointed to a series of effects common for large groups of living organisms, e.g. arteriosclerosis in mammals. Even if most of these effects seem to depend rather strongly on time, it is clear that the organism is originally able to handle these complications, since otherwise the accumulation of these effects would probably have been lethal much earlier. Perhaps ageing can best be described as an expression for the organisms increasing loss of control of the entire metabolism, and the phenomenon should then be traced back to the inability to produce the enzymes necessary to regulate the normal processes. It seems hence very likely that the ageing may primarily be due to a change of the genetic information.

Such a theory of ageing was in 1959 proposed by Szilard [79], who assumes that the genes are subject to random "ageing hits" which make them inactive with respect to the synthesis of a specific protein having a certain catalytic activity. By assuming that the probability, that a chromosome of a cell suffers an "ageing hit" per unit time, is a constant which is the same for all chromosomes, Szilard could make an interesting study of the ratio of boys and girls, at birth, as a function of the age of the father.

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79) L. Szilard, Proc. Nat. Acad. Sci. U.S. 45, 30 (1959); Nature 186, 649 (1960).

Let us now study the problem of ageing from the point of view that the genetic code is carried by the DNA-molecule. It should first of all be observed that the gamates, the eggs and the sperms, are as a rule taken aside at an early stage of the life of an organism. The material in the other parts of the body of an organism is constantly renewed at a certain rate characteristic for the species and the types of cells involved, which means that the somatic cells are undergoing repeated cell replications (mitosis). The quantum-mechanical analysis of the genetic code in the Watson-Crick model has shown that, depending on the "tunnel effect", a "pure" genetic message does not exist, and that there is always a finite probability error built into even the ground state of the DNA-molecule. Since this error may cause a certain amount of loss of genetic information in each DNA-replication, it seems hence very likely that the phenomenon of ageing

would depend on the accumulation of such loss of genetic information.

The conclusion seems hence to be that the phenomenon of ageing of individual organisms depends essentially on the quantum-mechanical "tunnel effect". This effect is strictly time-dependent, and, it is probably not a mere coincidence that we practically measure also the age of archeological pieces and the earth itself by means of the same type of tunnel effect - namely the radioactivity. It should finally be mentioned that the disintegration of dead matter and particularly solid-state through corrosion is actually believed to depend on a tunnelling phenomenon.

9. SOME ASPECTS ON THE CONNECTION BETWEEN THE DNA-STRUCTURE AND THE DEVELOPMENT OF TUMORS AND CANCER

Spontaneous Tumors. - The growth of an individual is a highly refined balance between factors which enhance the cell duplication and other factors which limit this duplication so that the organism takes a specific shape. The entire process is stimulated and controlled by various enzymes, and there is a feed-back from the environment about which we know presently very little. If there is a somatic mutation, i.e. a change of the genetic code in a DNA-molecule in the body of an organism, the change may influence the protein synthesis and the balance between the enhancing and controlling enzyme actions in the growth cycle. Actually, the new genetic code may lead to the development of a "new individual" within the individual, i.e. a tumor [80].

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80) For a general survey of the problem, see e.g. "Carcinogesis, Mechanisms of Action", Ciba Found. Symp. 1958 (Churchill, London 1959).

Since the spontaneous somatic mutations apparently depend on the same quantum-mechanical "tunnel effect" as the ageing process, there ought to be a clear correlation between age and the occurrence of spontaneous tumors. This gives an explanation of the experimental fact that there seems to be an increasing probability for the occurrence of spontaneous tumors with increasing age.

If ageing may be described as the result of the accumulation of proton errors, the occurrence of tumors may depend on the fact that the accumulation has passed a certain limit in a particular direction.

It is evident that not all types of tumors have to be malignant. However, if the balance between the enzymes enhancing the DNA-replication and the cell duplication and the enzymes checking this process are disturbed in favor of the former, there may develop a malignant tumor. Cancer will here be described as the growth of such abnormal cells in the living organism as have a higher rate of metabolism than the normal cells and which hence may take over the normal material in large areas of the organism and form malignant tumors. In the deletion hypothesis [80], cancer is essentially assumed to be caused by the fact that the growth-controlling enzymes are deleted. This means that, if through proton tunnelling, the DNA-molecule loses its ability to regulate the synthesis of these specific enzymes, spontaneous cancer will develop. The occurrence of spontaneous cancer would, in this model, depend on a quantum-mechanical tunnel-effect of a statistical nature involving the movement of two protons over a distance of about 1 Å = 10^{-8} cm. One could then understand why cancer can occur at young age, but also why the probability goes up highly with increasing age.

It has been discussed whether cancer is a virus desease, since cancer may in certain cases be induced by injection of highly filtered extract from a cancer tumor on a healthy individual of the same species. Today, one can understand these experiments in terms of the "transformation principle" discussed in Sec. 2, and it is clear that the extract may contain DNA-molecules containing the carcinogenic message. Today, it seems rather unlikely that the main forms of cancer are originally caused by some external virus, i.e. by external RNA- or DNA-molecules in protein-overcoats existing in free form. It seems instead much more probable that the special "cancer virus" is of intracellular nature and consists of the organism's own RNA- or DNA-molecules with a distorted genetic message which enables them to change the protein synthesis in their favour and to take over the metabolism and cause cancer. This view explains also why the cancer pattern can be so easily transported within the organism and give rise to daughter tumors (metastasis).

If this view is correct, a great deal of precautions ought further to be necessary to see that such intracellular virus cannot be spread through injections. The problem remains also whether there could exist an external virus which could induce somatic mutations by having the effect of a mutagen. This problem will be treated further below.

Induced tumors. - In the treatment of the problem of carcinogesis, a theory has been developed [81] which contains two stages:

1) initiation
2) promotion

The initiation is usually assumed to consist of a somatic mutation, i.e. a change of the genetic code in DNA, induced by chemicals, by radiation, or by other means. It should be observed that, even if the new code does not contain a highly carcinogenic message, one may further disturb the balance between the growth-enhancing and the growth-controlling enzymes by means of suitable chemicals during the promotion stage. This may start the growth of a malignant tumor, and the new environment may then be sufficient to permit a chain reaction to develop. The treatment of the promotion is essentially outside the framework of this paper, and we will confine outselves to consider only the somatic mutations.

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81) See e.g. A.L. Walpole, reference 80, p. 41.

Somatic mutations may be induced by essentially the same mechanisms as ordinary mutations, i.e. by chemicals, by radiation, and by certain other physical means. The chemicals should have the property of being transferred to the region of the DNA-replication, and one can hence expect that a special group is formed by those which may be easily attached to the proteins which catalyze this replication.

It is today not known whether there are any external viruses which may act as mutagens, but the possibility should certainly be observed.

An extensive theoretical study of the carcinogenic activity of the catacondensed hydrocarbons has been carried out by the two groups in Paris under Pullman and Daudel [82]. By investigating the connection between charge

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82) For a survey of the early literature in this field, we would like to refer to the review by C.A. Coulson, Adv. Cancer Res. 1, 1 (1953).

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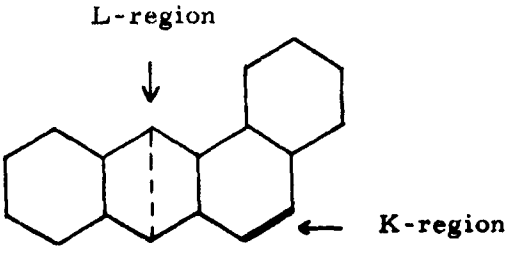
and bond orders and carcinogenic activity, the Pullmans [83] have found that there are two regions of special interest in these hydrocarbons denoted as

83) For a survey, see e.g. A. Pullman and B. Pullman, Adv. Cancer Res. 3, 117 (1955); Revs. Modern Phys. 32, 428 (1960); "Quantum Mechanical Methods in Biochemistry" (to be published in 1962).

K- and L-regions:



and that the molecule is carcinogenic if the chemical activity in the K-region is sufficiently high and the activity in the L-region is sufficiently low. Experiments by Heidelberger [84] have indicated that these conditions may be connected with the ability of the molecules to get attached to certain proteins. Since molecules of this type may enter electronic donor-acceptor reactions with the nucleotide bases, one can expect that they may induce mutations if they reach the immediate neighbourhood of the DNA-molecule. Little is known about the actual mechanism, however, and it should be observed that this theoretical study was started in Paris before the important role of the nucleic acids in genetics was realized. The information was gained solely by studying the correlation between electronic structure and carcinogenic activity, and the results achieved in this way are remarkable.

84) C. Heidelberger, reference 80, p. 179.

The inducing effect of radiation on somatic mutations seems to depend on ionization, essentially in the same way as in the ordinary mutations. Again the genetic code is disturbed by proton tunnelling and, under certain circumstances, a carcinogenic message may result.

It is interesting to observe that, if the electrostatic picture of the hydrogen bonding is true, one can expect that an outer electrostatic potential may induce proton tunnelling and disturb the genetic message. This is a clear physical effect without any chemical interaction, and it could be caused, for

instance, by means of a dipole-layer introduced for a sufficiently long time in a tissue. Since plastic films are often statically charged - they are technically used as "electrets" - and metals in liquids assume electrochemical potentials, one could expect to obtain results with rather small means. However, whether there is a definite correlation between these electrostatic effects and Oppenheimer's experimental results [85] concerning the high carcinogenic activity of plastic films and certain metals embedded in small sheets in tissues is too early to say, but the connection seems certainly interesting and worthwhile investigating. It should be observed that no carcinogenic effect was obtained if the plastic material was introduced as a powder, so it seems as if the effect would have a physical origin.

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85) P. Alexander and E.S. Horning, reference 80, p. 12.

The medical treatment of cancer has to depend on the difference between cancer cells and the normal cells. It has been found that the former are more sensitive to radiation than the latter, and this may depend on the fact that the radiation causes additional errors in the base sequences of the DNA-molecules involved, and that a too large deviation from the normal sequence may lead to DNA-molecules, which are not reproducible by a growth cycle. However, the radiation influences the growth cycle and the metabolism in many other ways, and it would be interesting to study the absorption spectrum of cancer cells or nuclei in comparison to normal cells or nuclei to see whether one could get more selective effects by limiting the radiation to specific frequences or by making it "monocromatic".

The chemotherapy of cancer has to be directed towards stopping the growth cycle of the cancer cells leaving the normal cells as little damaged as possible. Again the base sequences of the DNA- and RNA-molecules are probably the weakest points of the cancer cells, and by introducing "base analogs", i.e. bases similar to the normal bases buth without the proper action in the protein synthesis, as nutrition material in the cancer cells, one can hope to stop their duplication. The base analogs should be such that they are accepted as normal building material in the DNA duplication, but they should then be inactive in the formation of RNA leading to errors deactivating the protein-synthesis, or they should show a tendency to destroy the proton code; see Sec. 7. The difficulties are here connected with the fact that many "base analogs" are highly poisonous

also to the normal cells. Even other points in the cancer metabolism may be attacked by suitable chemicals, e.g. the enzyme actions, and, in connection with induced cancer, the stage of promotion should be given particular attention.

Other differences between the cancer cells and the normal cells, e.g. a difference in permeability of their membranes, may be used to prepare the cancer cells for the final attack by radiation, base analogs, or other chemicals. The difficulty in all medical treatments of cancer lies in the fact that, if a single cancer cell or erroneous DNA-molecule is left, the cancer pattern may develop again as it started.

Our study makes it to a certain extent rather likely that the ultimate cause of spontaneous cancer - the "principle of cancer" - may be a quantum--mechanical phenomenon associated with two protons changing their places over a distance of the order of magnitude of 10^{-8} cm through a potential barrier by means of the tunnel effect. However, it may hardly be emphasized that the model of the cause of cancer described here may be highly oversimplified. The DNA-molecule may contain the essential genetic information, but also RNA--molecules and proteins are inherited by the daughter cells after a cell duplication. The protein-synthesis and its feed-back on the cell duplication is a highly complicated biochemical process of which one has only a limited knowledge, and many points may here be relevant also in connection with cancer. However, the model is so striking in its simplicity that it may well be worthwhile to give it a careful theoretical study.

10. DISCUSSION

Summary. - Let us now summarize the main points discussed in this paper. Deoxyribonucleic acid (DNA) is considered as the hereditary substance and, according to Watson-Crick's model, the genetic message is contained in a proton-electronpair code which is situated well hidden and shielded in the middle of a double helix. The code consists actually of two complementary pieces of "lock and key"-type which together have a great deal of stability. The genetic information is transferred to the cell by means of the formation of messenger-RNA but, during the transcription procedure, the code is not opened up at all, and the message is instead read in an extra "copy" which nature has provided in the deep groove of the double helix. In the replication process,

the code is opened only momentarily to find the correct partners for the doubling of the genetic message. All these precautions give the genetic code an unusual stability and explain its ability to preserve a genetic message intact over thousands of years.

In this paper we have pointed out that, since the protons are not classical particles but "wave packets" obeying the laws of modern quantum theory, the genetic code cannot - in spite of all precautions - be 100 o/o stable. Due to the quantum-mechanical "tunnel effect", there is always a small but finite probability that the protons will change place, alter the genetic code, and give rise to mutations. This implies also that this transfer of protons over a distance of about 10^{-8} cm may be one of the driving forces in the evolution of living organisms on the earth. In an organism subject to renewal through repeated cell duplications, the same "tunnel effect" may lead to a loss of genetic information which may be the primary cause of the phenomenon of ageing. Since the proton tunnelling further leads to somatic mutations, the phenomenon may also be responsible for the occurrence of spontaneous tumors and cancer.

It is evident that a model of these biological phenomena where all the emphasis is put on the DNA-molecule must be somewhat oversimplified, since there are certainly also other cell constituents which play an important role in these connections. We believe, however, that the picture serves a meaningful purpose as a first approximation.

Molecular Biology and Quantum Biology. - A few words should be added about the implications of the new approach of discussing biological phenomena on a molecular and sub-molecular level. It is clear that there is a considerable "language difficulty" depending on the fact that the terminology and conceptual structure developed in one field, say on the level of cellular organization, may not at all be convenient for the description in another field, say on the molecular level. Part of the importance of the Watson-Crick model lies just in the fact that it tries to bridge the gap between the life sciences and molecular theory.

During the last three decades, there has been a very strong tendency towards the unification of all the natural sciences. The development has also shown that many important achievements in medicine depend on the basic research carried out in the new field of molecular biology. From the point of view of health, the living systems are essentially nothing but huge chemical systems, which are in their normal or abnormal behaviour subject to the laws

of physics and chemistry. In the recent development of the biosciences, more and more emphasis has been put on the fundamental molecular structure of the living systems and on the detailed electronic and protonic structure of the molecules involved. The Pullmans [76] have pointed out that the flexibility and the extremely high mobility of the living systems seem in many cases to be connected with the properties of the "mobile electrons" of the conjugated systems, which occur as essential constituents in the giant molecules in the living systems.

The electrons and protons are fundamental particles which do not obey the laws of classical physics but the laws of modern quantum mechanics. The electronic and protonic structure of biologically interesting molecules has hence to be treated by quantum chemistry, and this seems to lead to the opening of a new field which should perhaps be called "quantum biology". The principles of quantum mechanics are of fundamental importance for treating not only the ground state and the excited states of conjugated systems and polynucleotides, but also the biologically interesting molecules in general, the problem of energy storage and energy transfer, and many other basic problems in biophysics and biochemistry, which are now treated under the common name of "submolecular biology" [86]. The modern theory of the structure of matter has through quantum mechanics rendered a unification of the fundaments of physics and chemistry which was previously inconceivable, and it seems as if the biosciences would be next in turn to join the same basis.

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86) The need for the development of a submolecular biology has been particularly strongly emphasized by A. Szent-Györgyi, "Introduction to Submolecular Biology" (Academic Press, 1960); see also M. Kasha and B. Pullman, "Horizons in Biochemistry", Albert Szent-Györgyi Dedicatory Volume, (Academic Press, 1962); R.B. Setlow and E.C. Pollard, "Molecular Biophysics" (Addison-Wesley 1962).

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Special thanks should finally be expressed to Prof. B. Pullman and Dr. A. Pullman for many valuable and stimulating discussions on these problems during the Summer Institute in Quantum Chemistry and Solid-State Physics in Uppsala in 1962.

The main ideas of this paper have been expressed in some lectures during the summer of 1962 on quantum genetics and the structure of DNA: at the Escuela Nacional de Agricultura, Chapingo, Mexico in July, at the Summer Institute in Quantum Chemistry and Solid State Physics in Uppsala in August, at the Symposium on Large Molecules in Kyoto, Japan, in September, and at the Symposium on Molecular Structure and Spectroscopy, Tokyo, Japan, also in September.

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1.	Per-Olov Löwdin and Hiroyuku Yoshizumi	Correlation Problem in Many-Electron Quantum Mechanics. A survey of the Development and a Discussion of some Current Ideas. June 21, 1957. (Published in Advances in Chemical Physics, ed. I. Prigogine 2, 207, 1959).
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3.	J.O. Hirschfelder and Per-Olov Löwdin	The Long-Range Interaction of Two 1s Hydrogen Atoms Expressed in Terms of Natural Spin Orbitals. August 20, 1957. (Published in Molecular Physics 2, 229, 1959).
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7.	Per-Olov Löwdin	Generalization of the Hartree-Fock Scheme. February 20, 1958. (Published in Ann. Acad. Reg. Sci. Upsaliensis 2, 127, 1958).
8.	A.J. Freeman and Per-Olov Löwdin	On a Quantum Mechanical Kinetic Energy Transformation. March 20, 1958. (Published in Phys. Rev. 111, 1212, 1958).
9.	Harrison Shull and Per-Olov Löwdin	Variation Theorem for Excited States. April 1, 1958. (Published in Phys. Rev. 110, 1466, 1958).
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	11.	Per-Olov Löwdin	An Elementary Iteration-Variation Procedure for Solving the Schrödinger Equation. April 23, 1958. (Acc. for publ. J. Mol. Spect.)
	12.	Per-Olov Löwdin	Angular Momentum Wave Functions Constructed by Projection Operators. May 10, 1958.
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*	14.	Per-Olov Löwdin	Degeneracies of Atomic dn Configurations Treated by Projection Operator Formalism. July 15, 1958.
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*	17.	Harrison Shull	The Two-Electron Homopolar Chemical Bond; Hydrogen. September 15, 1958.
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*	19.	H. McIntosh	Symmetry-Adapted Functions Belonging to the Symmetric Groups. October 6, 1958. (Published in J. Math. Phys. 1, 453, 1960).
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*	21.	H. McIntosh	Towards a Theory of the Crystallographic Point Groups. November 3, 1958. (Published in J. Mol. Spectroscopy 5, 269, 1960).
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26.	Harrison Shull	The Nature of the Two-Electron Chemical Bond. I. The Homopolar Case. June 5, 1959. (Published in J. Am. Chem. Soc. 82, 1287, 1960).
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30.		Report from the International Summer Institute in Quantum Chemistry held at Skogshem, Lidingö, in 1959.
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32.	J. Linderberg and H. Shull	Electronic Correlation Energy in 3- and 4--Electron Atoms. November 1, 1959. (Published in J. Mol. Spectroscopy 5, 1-16, 1960).
33.	G.G. Hall	Improved Atomic Wave Functions Using a Functional Transformation. November 20, 1959. (Published in Proc. Phys. Soc. LXXV, 575, 1960).
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37.	J. de Heer and R. Pauncz	Molecular Electronic Integrals for Cyclic Systems. February 15, 1960. (Published in J. Mol. Spectroscopy 5, 326, 1960).
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39.	J.L. Calais and J. Linderberg	Atomic Angular Momentum Wave Functions for the Configurations $s^n p^m$ in the Cases of Weak, Strong and Intermediate Coupling. Studied by the Projection Operator Technique. March 1, 1960.
40.	J. Linderberg	Exact Perturbation Treatment of Hartree--Fock Equations. March 1, 1960. (Published in Phys. Rev. 121, 816, 1961).
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QUANTUM GENETICS AND THE APERIODIC SOLID. Some aspects on the biological problems of heredity, mutations, ageing, and tumors in view of the quantum theory of the DNA molecule.

Per-Olov Löwdin November 11, 1962

ABSTRACT: The problems of mutations, ageing, and tumors are studied on the basis of tautomeric changes in Watson-Crick's model of DNA caused by proton tunnelling.

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